NEW JERSEY AIDS Line

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NJ Cross Part Collaborative Team Honored for Improving HIV Care

Jane Caruso, MS, NJDHSS

The NJ Cross Part Collaborative Team core members receive HRSA/ National Quality Center award.

Back row: Gail Johnson, Capital Health Systems, Maryann Andrews, Kennedy Health System; Ketlen Alsbrook, Newark EMA (Part A); Ellen Dufficy, NJDHSS Parts B and D; Sandra Houston, Hudson TGA; Karen Walker, Bergen-Passaic TGA; David Rosen; Kelly Rand, NY/NJAETC; Connie Mazzella, Jersey Shore Medical Center; Peter Oates, FXB Center-UMDNJ; Pam Gorman, Cooper University Hospital Seated: Joy Robinson, Eric Chandler Clinic; Terri Fox, Middlesex TGA; Dr. Sindy Paul, NJDHSS Part B; Jane Caruso, NJDHSS Part D.

THE New Jersey Cross Part Collaborative Team core members, pictured above, guided the cross part collaboration process in the State of New Jersey through an 18-month project to measure five critical HRSA-HAB indicators. One significant outcome of this endeavor was the improvement of syphilis screening rates among HIV+ patients from a low of 58% to a high of 76%. This was accomplished because of the diligent participation of EVERY New Jersey agency that receives Ryan White funds to provide HIV medical care. Grantees shared successful PDSA cycle information and best practice results, and technical assistance was readily available when requested.

At the close of this 18-month project, the State of New Jersey was recognized and honored by both HRSA and the National Quality Center, which jointly presented an award to the Team members in Washington DC on April 27, 2010. This award was given to the State of New Jersey for "The effective implementation of a statewide quality improvement project which resulted in measurable improvements for people living with HIV/AIDS across New Jersey."

The second phase of this collaborative has recently been drafted with input from the Ryan White medical providers of New Jersey and the guidance of HRSA Officers and the National Quality Center. The Team is looking forward to a sustainable statewide quality project, and has begun efforts to circulate information about the new project.

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CE Continuing Education

CME/CE Article No. 1

CME /CE Article #2

Resources

CONTINUING EDUCATION

HIV Treatment Guidelines and Cautions, and the Role of the Pharmacist in Care

Release Date: June 1, 2010 • Expiration Date: June 30, 2012 • Course Code: 12HC01-DE01 • Nursing Credit for this activity will be provided through June 30, 2012.

Sponsor

Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ), Center for Continuing & Outreach Education, Division of AIDS Education.

Funding

This activity is supported by an educational grant from the New Jersey Department of Health and Senior Services (NJDHSS) - Division of HIV/AIDS Services through a MOA titled "Education and Training for Physicians and other Healthcare Professionals in the Diagnosis and Treatment of HIV/AIDS." The New York/ New Jersey AETC (AIDS Education and Training Center (NY/NJAETC) provided in-kind support through the work of its Pharmacy Director, John Faragon, PharmD, BCPS, AAHIVE.

Target Audience

This application-based activity is designed for physicians, nurses, pharmacists, and other health care professionals in New Jersey who are involved in the care of persons with HIV/AIDS.

Statement of Need

The CDC and Infectious Disease Society of America (IDSA) issued updated antiretroviral treatment recommendations in December 2009,. Several agents have been reclassified as "not recommended" due to evidence of inferior virologic efficacy, high incidence of toxicities, and/or problems related to convenience.

The recommendations summarize findings of adverse effects and interactions between antiretroviral medications and other medical treatments.

Infectious disease clinicians may not have access to records allowing them to review all medications prescribed by other primary care and specialty care providers, to identify and avoid problematic combinations. Common treatments for tuberculosis, hyperlipidemia, seizure disorders, asthma, and many psychiatric illnesses have interactions with antiretroviral medications that may significantly increase or decrease concentration and risk under or overdosage. For example, iatrogenic Cushing's syndrome has been documented since 2002 in HIV-infected patients receiving ritonavir and inhaled fluticasone, but continues to be reported. HIV treatment should be planned to minimize interactions and adverse effects of combining HIV antiretroviral and other medications. The treatment team can include pharmacists, primary care providers, and specialists who also provide care to the same patient.
http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Learning Objectives

Upon the completion of this activity, participants should be able to:

1. List preferred, alternative/ acceptable and regimens not recommended that are included in the December 2009 revision on the Department of Health and Human Services (DHHS) Guidelines for HIV treatment.
2. Provide examples of common medications used in the primary care setting that should be avoided in patients receiving HIV treatment.
3. Describe the role of the pharmacist in HIV care.
4. Reduce medication errors through use of guidelines and/or pharmacist consultation.

Faculty

John Faragon, PharmD, BCPS, AAHIVE is a pharmacist at Albany Medical Center in Albany, NY, and NY/NJAETC Regional Pharmacy Director.

Activity Director(s)/CME Academic Advisor(s)

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Planning Committee

- **Sindy Paul, MD, MPH, FACPM,** Medical Director, Division of HIV/AIDS Services, NJ Dept. of Health and Senior Services
- **Debbie Y. Mohammed, MS, APRN-BC, ACRN,** Nurse Practitioner, UMDNJ-University Hospital and St. Michael's Medical Center – Peter Ho Clinic
- **Kimi Nakata, MSW, MPH,** UMDNJ-CCOE-Division of AIDS Education Program Supervisor and NJ AIDSLine Editor
- **John Faragon, PharmD, BCPS, AAHIVE;** NY/NJ AETC Clinical Pharmacy Director; pharmacist, Albany Medical Center

Method of Participation

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test which consists of a series of multiple-choice questions. Upon completing this activity as designed and achieving a passing score of 70% or more on the self-assessment test, participants will receive a letter of credit and the test answer key four (4) weeks after receipt of the self-assessment test, registration, and evaluation materials; or may complete the activity on the internet at www.umdnj.edu/ccoe. Estimated time to complete this activity as designed is 1.25 hours for physicians and pharmacists, and 1.33 hours for nurses.

Accreditation

Physicians: UMDNJ-Center for Continuing and Outreach Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

UMDNJ-Center for Continuing and Outreach Education designates this educational activity for a maximum of 1.25 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses: UMDNJ-Center for Continuing Education and Outreach Education is an approved provider of continuing nursing education by NJSNA, an accredited approver, by the American Nurses Credentialing Center's Commission on Accreditation. Provider Number P173-11/09-12. Provider Approval is valid through November 30, 2012.

This activity is awarded 1.33 contact hours. (60 minute CH)

Provider approved by the California Board of Registered Nursing, Provider Number CEP 13780.

Pharmacists: UMDNJ-Center for Continuing and Outreach Education is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

This course (ACPE # 0374-1000-10-100-H02-P) qualifies for 1.25 contact hours (0.125 CEUs) of continuing pharmacy education credits.

Pharmacists and nurses should only claim those contact hours actually spent participating in the activity.

Review: This activity was peer reviewed for relevance, accuracy of content, and balance of presentation by Patricia Kloser, MD, MPH; Debbie Mohammed, MS, MPH, APRN-BC, AACRN; Humberto Jimenez, PharmD, AAHIVE, Clinical Assistant Professor, Ernest Mario School of Pharmacy, Rutgers University; and Brenda Christian, MEd, PA-C; Director of AIDS Education, UMDNJ-CCOE; and pilot tested for relevance and time required for participation by Kinshasa Morton, MD; Shobha Swaminathan, MD; Bonnie Abedini, MSN, RN; Mary C. Krug, MSN, APN; Kara Winslow, BSN, RN; Polly Jen, PharmD, and George Rusuloj, PharmD.

Disclosure Disclaimer

In accordance with the disclosure policies of UMDNJ and to conform with ACCME and FDA guidelines, individuals in a position to control the content of this education activity are required to disclose to the activity participants: 1) the existence of any relevant financial relationship with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients, with the exemption of non-profit or government organizations and non-health care related companies, within the past 12 months; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Disclosure Declarations

There were no relevant financial relationships to disclose reported by the activity director, faculty, planning committee members, editor, content reviewers or field testers.

Off-Label Usage Disclosure

This activity does not contain information of commercial products/devices that are unlabeled for use or investigational uses of products not yet approved.

Content Disclaimer

The views expressed in this activity are those of the faculty. It should not be inferred or assumed that they are expressing the views of NJDHSS-Division of HIV/AIDS Services, UMDNJ, or any manufacturer of pharmaceuticals. It should be noted that the recommendations made herein with regard to the use of therapeutic agents, varying disease states, and assessments of risk, are based upon a combination of clinical trials, current guidelines, and the clinical practice experience of the participating presenters. The drug selection and dosage information presented in this activity are believed to be accurate. However, participants are urged to consult the full prescribing information on any agent(s) presented in this activity for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects before prescribing any medication.

NEW JERSEY AIDSLine June 2010

HIV Treatment Guidelines & Cautions, and the Role of The Pharmacist in Care

John J. Faragon, PharmD, BCPS, AAHIVE

LEARNING OBJECTIVES

Upon completion of this activity, participants should achieve the following:

1. List preferred, alternative/acceptable and regimens not recommended that are included in the December 2009 revision on the Department of Health and Human Services (DHHS) Guidelines for HIV treatment.
2. Provide examples of common medications used in the primary care setting that should be avoided in patients receiving HIV treatment.
3. Describe the role of the pharmacist in HIV care.
4. Reduce medication errors through use of guidelines and/or pharmacist consultation.

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Release Date: June 1, 2010 • Expiration Date: June 30, 2012 • Course Code: 12HC01-DE01 • Nursing Credit for this activity will be provided through June 30, 2012.

John J. Faragon, PharmD, BCPS, AAHIVE is a Pharmacist at Albany Medical Center Hospital, Albany, NY and Regional Pharmacy Director – New York New Jersey AIDS Education and Training Center

Sponsor: UMDNJ-Center for Continuing & Outreach Education-Division of AIDS Education.

Funding: This activity is supported by an educational grant from NJDHSS Division of HIV/AIDS Services through MOA titled "Education and Training for Physicians and other Healthcare Professionals in the Diagnosis and Treatment of HIV/AIDS. Pharmaceutical review was provided in-kind through the New York/ New Jersey AETC.

To obtain continuing education credit, complete the quiz, registration, and evaluation on the following pages, or go to: www.umdnj.edu/ccoe/aids

DHHS GUIDELINES OVERVIEW

What To Start With

The Department of Health and Human Services updated the guidelines for the initial treatment of HIV-infected adults and adolescents in December, 2009. [1]

Four Preferred Regimens for Treatment-Naiive Patients

NNRTI-based Regimens

- **Efavirenz/tenofovir/emtricitabine**

PI-based Ritonavir-boosted Regimens

- **Darunavir/ritonavir**
- **Atazanavir/ritonavir**

New:

Integrase Inhibitor (INSTI)-based Regimen

- **Raltegravir + tenofovir/emtricitabine**

See Table 1 for details.

ONE OF THE MAIN CHANGES that occurred with this guideline was that the preferred, recommended regimens for treatment-naïve patients were reduced to only four regimens.

- The **preferred** non-nucleoside based regimen remains the combination of **efavirenz/tenofovir/emtricitabine;** the preferred protease inhibitor regimens include **atazanavir/ritonavir and darunavir/ritonavir.** The new guidelines added the integrase inhibitor **raltegravir** on the preferred list as an additional option for initial treatment of HIV infection.

WITHIN THE PROTEASE INHIBITOR CLASS OF MEDICATIONS, the guideline committee narrowed the preferred selection to 2 PIs for initial treatment.

- Once-daily darunavir/ritonavir (dosed as 800 mg/100 mg, respectively) in combination with tenofovir and emtricitabine.
- Once-daily atazanavir/ritonavir in combination with tenofovir and emtricitabine .
- Lopinavir/ritonavir was removed from the preferred list and became an alternative, except in the setting of pregnancy.
- During pregnancy, twice-daily lopinavir/ritonavir in combination with zidovudine/lamivudine is the only preferred regimen.
- Fosamprenavir/ritonavir was also moved from preferred status to an alternative for HIV treatment.
- The preferred options for HIV treatment now include the integrase inhibitor raltegravir, given twice daily in combination with once-daily tenofovir/emtricitabine.

The guideline committee has narrowed the preferred options to four treatment regimens.

The rationale for these changes is based upon numerous data sets.

- The NNRTI, triple-drug combination tablet containing efavirenz/tenofovir/emtricitabine [Atripla] remains the **standard of care for NNRTIs** given its efficacy, tolerability and convenience.[2]
- For patients who are pregnant, intending to become pregnant or those who are not using effective contraception, efavirenz-based regimens should be avoided.[3]
- For the boosted PI options, recent data suggests that higher doses of ritonavir (at total daily doses of 200 mg or greater) lead to increased rates of gastrointestinal adverse events and of metabolic complications, including hyperlipidemia, in studies of treatment-naïve patients.[4,5,6,]

  For example, once-daily darunavir/ritonavir and once-daily atazanavir/ritonavir based regimens have both demonstrated lower incidence of hyperlipidemia and gastrointestinal adverse events when compared to twice-daily lopinavir/ritonavir based regimens.[7,8]
- Atazanavir and darunavir require only 100 mg of ritonavir once daily for boosting, whereas the use of lopinavir/ritonavir will require a total of ritonavir 200 mg a day.
- Both darunavir/ritonavir and atazanavir/ritonavir have demonstrated either statistical non-inferiority or superiority to lopinavir/ritonavir based regimens.[7,8]
- As a result, the panel removed lopinavir/ritonavir and fosamprenavir/ritonavir from the preferred list of initial HIV regimens and reclassified it down to an alternative option.[1]

The DHHS Guideline revision also provided guidance on preferred regimens to use when treating HIV during pregnancy.

- Based on data from maternal to child transmission studies and length of experience using these medications in pregnancy, the **only preferred regimen in this setting is twice daily lopinavir/ritonavir in combination with zidovudine/lamivudine.**
- Some clinicians may increase dosage to three tablets, twice daily, due to the increase in a pregnant woman's volume of distribution in the third trimester.[1,9,10]

In a study of efavirenz/tenofovir/emtricitabine compared to twice daily raltegravir in combination with tenofovir/emtricitabine, similar efficacy was demonstrated for both of these regimens at 48 weeks.

- There was also a lower incidence of CNS adverse events and lipid abnormalities reported in the raltegravir arm compared to the efavirenz. As a result the panel now recommends this as a preferred regimen in naïve subjects.
- At this time there is no data comparing an integrase inhibitor with a boosted PI.
- Raltegravir also has a relatively low genetic barrier to resistance, making it an unfavorable option in a patient who is not consistently adherent.
- Finally, raltegravir has not been studied extensively with NRTI combinations other than tenofovir/emtricitabine.[11]

The NNRTI, triple drug combination tablet containing:

- **efavirenz**
- **tenofovir**
- **emtricitabine [Atripla]**

remains the standard of care for NNRTIs given its efficacy, tolerability and convenience.

Although the guideline committee has narrowed the preferred options to four treatment regimens, there are other regimens that remain acceptable alternatives in select patients.

- In addition to preferred status, the guidelines also classify other regimens as either alternative, acceptable, or acceptable but require additional data.
- Though many of these regimens are effective, they all have some disadvantage when compared to preferred regimens.
- These disadvantages include differences in tolerability, convenience and virologic efficacy.

Tables 1, 2 and 3 list the preferred, alternative and acceptable regimens from the DHHS Guidelines.[1]

(Continued on next page)

Figure 1

Antiretroviral Medication Reference List

1. Reverse transcriptase inhibitors ("Nukes"): The first anti-HIV drugs. They block reverse transcription (the creation of viral DNA from RNA) by providing "decoy" building blocks that interrupt the process. Most are nucleoside analogs; tenofovir is a nucleotide analog.

Generic Name	Trade Name	Alternate names
Zidovudine	Retrovir	AZT, ZDV
Didanosine	Videx	ddI
Stavudine	Zerit	d4T
Lamivudine	Epivir	3TC
Zidovudine/Lamivudine	Combivir	AZT + 3TC
Abacavir	Ziagen	ABC
Zidovudine/Lamivudine/Abacavir	Trizivir	AZT + 3TC + ABC
Tenofovir	Viread	TDF
Emtricitabine	Emtriva	FTC
Abacavir/Lamivudine	Epzicom	ABC + 3TC
Emtricitabine/Tenofovir	Truvada	FTC + TDF

2. Non-nucleoside reverse transcriptase inhibitors: these also interrupt reverse transcription, by binding to the reverse transcriptase enzyme and restricting its activity.

Generic Name	Trade Name	Alternate names
Nevirapine	Viramune	NVP
Delavirdine	Rescriptor	DLV
Efavirenz	Sustiva	EFV
Etravirine	Intelence	ETR

3. Protease inhibitors: Block the action of protease, an enzyme that cuts HIV protein chains into specific proteins needed to assemble a new copy of the virus. NOTE: when you see "/r" after the name of a protease inhibitor, that means it is boosted with a small dose of ritonavir. For example, SQV/r means saquinavir boosted with ritonavir. At present, only lopinavir and ritonavir are available in a single pill.

Generic Name	Trade Name	Alternate names
Saquinavir	Invirase	SQV
Ritonavir	Norvir	RTV
Indinavir	Crixivan	IDV
Nelfinavir	Viracept	NFV
Lopinavir/ritonavir	Kaletra, Aluvia	LPV
Atazanavir	Reyataz	ATV
Fosamprenavir	Lexiva	FPV
Tipranavir	Aptivus	TPV
Darunavir	Prezista	DRV

4. Integrase inhibitors: Block the action of integrase, an enzyme that inserts the viral DNA into the infected cell's DNA strands.

Generic Name	Trade Name	Alternate names
Raltegravir	Isentress	RAL

5. Fusion Inhibitors: Prevent HIV from attaching to outside of CD4 cell

Generic Name	Trade Name	Alternate names
Enfuvirtide	Fuzeon	T-20
Maraviroc	Selzentry	MVC

Adapted from: New Mexico AIDS Education and Training Center. Fact Sheet 409: Combination Medications. http://www.aidsinfonet.org

DHHS GUIDELINES OVERVIEW

When To Treat

ANOTHER SIGNIFICANT CHANGE to the guidelines was the decision of when to treat HIV infection in treatment-naïve adults and adolescents.

- The panel now recommends initiating ARV therapy at earlier CD4 thresholds than previous versions of the guidelines. In all patients with either a history of an AIDS-defining illness or with CD4 counts <350 cells/mm^3, antiretroviral therapy should be initiated.
- The current guidelines also recommend initiating therapy in HIV-infected patients with CD4 counts between 350 and 500 cells/mm^3.
- The panel was split 50:50 on recommending ARV for HIV-infected patients with CD4 counts over 500 cells/mm^3.
- Patients who have HIV-associated nephropathy or Hepatitis B co-infection should be started on ARV therapy regardless of CD4 count.
- All pregnant HIV-positive women should receive antiretroviral treatment to prevent perinatal HIV transmission. Decisions about the initiation and continuation of ARV therapy should be based on the standard guidelines for non-pregnant adults, with review of the safety and appropriateness of the regimen for both treatment and prophylaxis. For pregnant women with HIV infection who have never received antiretroviral treatment, and do not meet the standard guidelines for treatment, clinicians may consider delaying initiation of prophylaxis of until after the first trimester of pregnancy.[10]
- The decision to treat earlier comes from data sets that demonstrate that delaying therapy in patients with HIV infection increases the risk of death from non-HIV related causes.[12,13] These results suggest that the inflammation caused by ongoing viral replication, regardless of CD4 counts, increases mortality from non-HIV related diseases such as cardiovascular disease, renal disease, and liver disease. Treating earlier may also result in reduced rates of HIV transmission.[1]

ARV Regimens/Components Not To Be Offered at ANY Time

The preferred antiretroviral regimens for HIV treatment have changed dramatically since the initial version of the DHHS guidelines. Many regimens and components of regimens that were used years ago for managing HIV infection are no longer recommended either due to inferior virologic efficacy, high incidence of toxicities, or problems related to convenience.

(Continued on next page)

- Monotherapy or Dual Therapy with NRTI or NNRTI
- Triple NRTI Regimens (EXCEPT for Abacavir + lamivudine + zidovudine or possible tenofovir + zidovudine + lamivudine)
- Atazanavir and Indinavir
- Didanosine and Stavudine
- Dual NNRTI Combinations
- Efavirenz in 1st trimester of pregnancy or in women of significant child bearing potential
- Etravirine + ritonavir boosted atazanavir or fosamprenavir or tipranavir
- Emtricitabine and lamivudine
- Etravirine + unboosted PIs
- Nevirapine in treatment-naïve women with CD4>250 or in men with CD4>400
- Stavudine and Zidovudine
- Unboosted darunavir, saquinavir or tipranavir

ARV Regimens/Components *Not To Be Offered at ANY Time*

Monotherapy or Dual Therapy with NRTI or NNRTI

Due to the potential for rapid development of HIV resistance and inferior virologic efficacy, patients should NOT be receiving monotherapy with NRTIs or NNRTIs.

Though data has been presented on the use of various ritonavir boosted PI monotherapy (i.e.: lopinavir/ritonavir, atazanavir/ritonavir, darunavir/ritonavir), **use of these medications as the sole medication for treating HIV infection should only be done with close observation or in the setting of a clinical trial.**[14-17] The only place where monotherapy may be acceptable is when zidovudine is used for the prevention of perinatal HIV transmission.[9,10]

Though at one point recommended by guidelines, dual nucleoside regimens (e.g., zidovudine/lamivudine or tenofovir/emtricitabine) alone should be avoided due to the risk of virologic failure and the potential for the development of resistance.[1]

Triple NRTI Regimens

EXCEPT for Abacavir + lamivudine + zidovudine or possible tenofovir + zidovudine + lamivudine

Triple NRTI regimens were initially studied in HIV treatment due to their relatively low pill burdens, potential for once-daily dosing, and to avoid toxicities seen with PI or NNRTI-based regimens.

- However, clinical trial data in recent years has demonstrated that efficacy rates associated with triple NRTI regimens are not as good as other standard NNRTI or PI based regimens.
  For example, the triple NRTI regimens abacavir/tenofovir/lamivudine and tenofovir/didanosine/lamivudine (both once-daily regimens with low pill burden) were associated with early virologic failure when used in ARV-naïve patents.[18,19]
- Patients failing these regimens were also more likely to develop significant NRTI resistance. Triple NRTI regimens, in the absence of a PI or NNRTI, should be avoided in patients with HIV infection.

One potential exception is the use of the twice-daily triple combination of abacavir/zidovudine/lamivudine.

- In the ACTG 5095, this combination was shown to have efficacy, but was inferior to the regimen currently ranked as "alternative," efavirenz + zidovudine + lamivudine. When abacavir was added to the combination, it did not improve virologic response, leading to a conclusion that a 4-drug combination was not superior to a 3-drug combination.[1,21]
- Therefore, the use of abacavir/zidovudine/lamivudine, alone, should be avoided unless a PI or NNRTI cannot be used due to toxicities or concerns for significant drug interactions, as this regimen is considered inferior to preferred regimens.[1]

Atazanavir & Indinavir

The protease inhibitors atazanavir and indinavir are both **associated with the development of hyperbilirubinemia** and therefore, concurrent use of these medications together has the potential to **cause additive increases in bilirubin levels;** combination of these two medications should be avoided.[22]

Didanosine & Stavudine

In the mid to late 1990s, combinations including didanosine and stavudine were commonly used in many of our HIV treatment regimens.

- Recent understanding of the **significant toxicities** of these medications led the guidelines committees to recommend that concurrent use of didanosine and stavudine in ANY HIV regimen be avoided as stavudine and didanosine have been associated with **peripheral neuropathy, pancreatitis and hyperlactatemia.**[23]
- The recent understanding of the **overlapping toxicities** of these medications, including peripheral neuropathy, pancreatitis, and hyperlactatemia, let the guidelines panel to recommend against concurrent use of didanosine and stavudine in **ANY** HIV regimen.
- Their concurrent use in pregnant women has been associated with reports of **fatal cases** of lactic acidosis and hepatic steatosis.
- Providers should avoid this combination for HIV infected patients.[24]

ARV Regimens/Components *Not To Be Offered at ANY Time*

Dual NNRTI Combinations

Dual NNRTI combinations such as nevirapine and efavirenz with other nucleosides **should be avoided due to the high incidence of adverse events** when compared to nevirapine or efavirenz-based regimens alone.[25] In addition, since efavirenz and nevirapine are likely to reduce the concentrations of etravirine, concurrent use of these medications should also be avoided.[1,26]

Efavirenz in 1st trimester of pregnancy or in women of significant child-bearing potential

Efavirenz has been shown to be teratogenic in nonhuman primates and is classified as Pregnancy Category D.[3]

- In patients who are pregnant or of significant child-bearing potential, including those who are unreliable in using barrier contraception, **efavirenz should be avoided.**
- For women who are pregnant, the most recent update to the DHHS Guidelines for ARV recommends lopinavir/ritonavir twice daily in combination with zidovudine/lamivudine as the preferred initial regimen for pregnant women, those planning to become pregnant, and those who are assessed as unreliable users of effective contraception.[1]

Etravirine + ritonavir boosted atazanavir or fosamprenavir or tipranavir

Etravirine pharmacokinetic studies have demonstrated that the **concurrent use** of etravirine and either ritonavir boosted atazanavir, fosamprenavir or tipranavir **results in significant reductions in the boosted PI levels** and therefore these combinations should be avoided. If concurrent etravirine and boosted PI therapy is required, twice daily darunavir/ritonavir, lopinavir/ritonavir or saquinavir ritonavir are acceptable options.[1,26]

Emtricitabine and lamivudine

Emtricitabine and lamivudine are both cytosine analogues and therefore **should not be used together** due to the **risk of antagonistic interactions**.

Etravirine + unboosted PIs

Etravirine has not been studied in patients receiving regimens without boosted protease inhibitors. In addition, since it is an inducer of CYP450, it is likely to reduce the drug levels of unboosted PIs potentially compromising the effectiveness of the regimen. Therefore, the current guidelines do not recommend etravirine to be used concurrently with unboosted protease inhibitors such as indinavir, nelfinavir, unboosted atazanavir, or unboosted fosamprenavir.[1,26]

Nevirapine in treatment-naïve women with CD4>250 or in men with CD4>400

Nevirapine therapy has been associated with symptomatic (and even fatal) hepatotoxicity.

- Data demonstrates that hepatotoxicity is more likely to occur in ARV naïve women with CD4 counts >250 or in ARV naïve men with CD4 counts greater than 400.[1,27] Patients may also experience skin rashes, fever and flu like symptoms in the setting of hepatotoxicity. In rare cases, hepatotoxicity may continue to evolve even after discontinuation of the medication. Therefore, nevirapine should only be used within the recommended CD4 parameters with routine monitoring of hepatic function, unless the benefit outweighs the risk.
- Given recent changes to the CD4 thresholds for initiating HIV treatment to 500 cells/mm^3, the use of nevirapine in initial regimens should be considered only in select situations where other medications are not options.

Stavudine & Zidovudine

Stavudine and zidovudine should never be combined since zidovudine and stavudine are both thymidine analogues, they can compete for the same phosphorylation site in the growing chain of HIV DNA, resulting in an antagonistic, pharmacodynamic interaction.[28] Thus, **guidelines do not recommend their co-administration at any time.**[1]

Unboosted darunavir, saquinavir or tipranavir

Saquinavir in its current tablet formulation is not recommended to be used alone without ritonavir boosting since its drug levels likely to be inadequate for the effective treatment of HIV infection. Patients receiving saquinavir should also be receiving low dose ritonavir in addition to NRTIs if on this medication is being used. Similarly, darunavir and tipranavir have not been studied without ritonavir boosting and therefore should not be used alone.[1]

Antiretroviral Components *Not Recommended as Initial Therapy*

Co-formulated abacavir/lamivudine/zidovudine +/ - tenofovir

The ACTG 5095 study demonstrated that abacavir/zidovudine/lamivudine was inferior to both efavirenz plus abacavir/zidovudine/lamivudine AND efavirenz plus zidovudine/ lamivudine.[20] ■ As a result of this study, both the DHHS and the IAS-USA Guidelines removed abacavir/zidovudine/lamivudine from the preferred list of initial treatment in previous guideline revisions. ■ Therefore, the use of abacavir/zidovudine/lamivudine, alone, should be avoided as initial therapy as **this regimen is considered inferior to preferred regimens.** ■ Similarly, quad-nucleoside therapy with abacavir/zidovudine/lamivudine/tenofovir also demonstrated inferior virologic efficacy in initial treatment regimens and should be avoided as initial therapy.

Abacavir + didanosine or tenofovir

DUE TO LACK OF DATA IN INITIAL TREATMENT REGIMENS, the use of abacavir in addition to either didanosine or tenofovir should be avoided.[1]

Unboosted Darunavir

Unboosted darunavir has not been studied and should not be used in patients with HIV infection. All of the data leading to approval and subsequent preferred status on the DHHS Guidelines were based upon ritonavir boosted darunavir.[1]

Delavirdine

The NNRTI delavirdine should not be used in initial treatment regimens due to its inferior virologic efficacy in relation to other preferred initial regimens.

- Delavirdine is also dosed two to three times daily with a relatively large pill burden. Therefore, delavirdine is not recommended to be used in initial treatment regimens.[1]

Didanosine +Tenofovir

The use of didanosine and tenofovir as a nucleoside backbone should not be used in initial ARV regimens.

- This recommendation is based on clinical trial data in ARV naïve subjects that demonstrated **inferior virologic efficacy** when didanosine and tenofovir was combined with efavirenz.[19]
- Studies also have shown that when this combination is used, the **increase in CD4 counts** is often attenuated.[29]
- As a result, this combination should not be offered in initial treatment regimens.

Enfuvirtide

Due to the lack of data in treatment-naïve patients, the use of injectable enfuvirtide should be ***reserved for experienced patients*** with minimal treatment options remaining.[1]

Etravirine

Data supporting the use of etravirine in treatment-naïve patients is lacking. Therefore, this medication should ***only be used in treatment-experienced patients*** in combination with other ARV medications.[1, 26]

Indinavir (Unboosted or Boosted)

Unboosted indinavir should be avoided in ARV naïve subjects for several reasons: it needs to be taken on an empty stomach, requires three times daily administration, and requires patients to consume 1.5 liters of water daily.

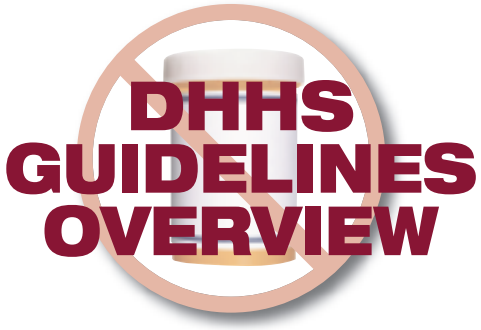
- Though ritonavir boosted indinavir can be taken twice daily, without regard for food, there is an **increased risk of nephrolithiasis** compared to unboosted indinavir in patients receiving this regimen.
- Due to the high pill burden associated with its use and the availability of better tolerated HIV regimens, its use is not recommended.[1]

Nelfinavir

Nelfinavir should be avoided in patients who are HIV infected due to its inferior virologic efficacy and its association with high rates of diarrhea.[4]

- Patients receiving this medication from years ago when it was the standard of care may continue the medication if their viral load remains suppressed, however its role in treatment-naïve patients or those who are treatment-experienced is limited and its use should be discouraged.[1]

Antiretroviral Components *Not Recommended as Initial Therapy*



Ritonavir as the sole Protease Inhibitor

Ritonavir as the sole protease inhibitor is dosed at 600 mg (6 x 100 mg capsules) twice daily. Gastrointestinal intolerance including diarrhea and nausea limit its use in initial treatment regimens. Lower doses of 100-200 mg one to two times daily are frequently used in combination with other protease inhibitors (with the exception of nelfinavir) to provide a pharmacokinetic boost which enhances drug levels. High dose ritonavir as the sole PI should be avoided in patients initiating therapy.

Unboosted Saquinavir

Unboosted saquinavir should not be used as initial therapy due to its **inferior efficacy** when compared to other standard NNRTI or boosted PI based regimens.[1]

Stavudine + lamivudine

Lamivudine has been associated with significant toxicities such as lipoatrophy, peripheral neuropathy, and hyperlactatemia.[23]

- Fatalities have also been reported with stavudine due to lactic acidosis, hepatic steatosis and pancreatitis.
- These medications should not be used as components of an initial ARV regimen.

Combinations of Antiretroviral & Other Meds *To Avoid*

Select Combinations To Avoid Due to Drug: Drug Interactions

The treatment of HIV infection is often complicated by drug-drug and drug-herbal interactions.

- In particular, the NNRTIs, the PIs and the CCR5 antagonist maraviroc are often most problematic since these drugs are extensively metabolized or are substrates of the CYP450 enzyme system.
- Though many medications can be used together with HIV medications, there are some that should be avoided. Some of these medications will be reviewed here, however, Table 5 lists medications that should be avoided with PI, NNRTI and CCR5 antagonists.
- Further data is also contained in updated tables in the DHHS guidelines which are an excellent reference for additional information on this subject.[1]

Antimycobacterial Medications

Concurrent management of either mycobacterium tuberculosis or mycobacterium avium complex in HIV-infected patients often leads to the potential for significant drug-drug interactions.

- The antimycobacterial medications rifampin, rifabutin, or rifapentine, are often used as part of an initial drug regimen to treat tuberculosis in HIV infection.
- However, due to its CYP450 induction properties, the use of rifampin with the protease inhibitors leads to significant reductions in PI drug levels by approximately 80-90%.[31,32]
- Despite these interactions, some HIV medications such as efavirenz and raltegravir may be used with dose modification.
- When using rifampin with efavirenz, current guidelines suggest that standard doses of rifampin be used, with increased efavirenz doses of 800 mg once a day.[1,32]
- However, in patients with lower body weight (<60 KG), efavirenz 600 mg may still be acceptable.[1,32]
- Raltegravir has also been studied with rifampin and has lead to reductions in raltegravir levels.
- The current label for raltegravir recommends that the raltegravir dosage be increased to 800 mg twice daily, with standard dose rifampin.[33]
- For patients requiring rifamycin therapy and receiving concurrent protease inhibitor-based therapy, the use of reduced-dose rifabutin is recommended as an alternative; dosing guidelines for rifabutin and protease inhibitor therapy should be consulted.[1,32]

Combinations of Antiretroviral & Other Meds TO AVOID

Ergot Alkaloids

Ergot alkaloids such as dihydroergotamine, ergotamine, ergonovir and methylergonovine *should be avoided in patients receiving PIs, NNRTIs, or CCR5 antagonists due to case reports of ergotism.*

Fluticasone

When fluticasone is given as either the nasal or the oral inhaler in combination with ritonavir, it has been associated with cases of severe adrenal suppression and Cushing Syndrome in children and adults, as a result of CYP3A4 inhibition associated with ritonavir. [33,34]

- Since fluticasone is also metabolized by the same enzyme, ritonavir increases fluticasone concentrations.[45] Therefore, patients receiving ritonavir as part of a boosted PI regimen should not use inhaled fluticasone nasal or oral inhalers.[1,45]
- Beclomethasone has been shown not to be metabolized by CYP3A4 and therefore will not result in the same interaction.
- Until further pharmacokinetic research is completed with other inhaled steroids, caution is recommended when ANY inhaled or nasal steroid is combined with ritonavir boosted protease inhibitor regimens.

Proton Pump Inhibitors

The absorption of atazanavir requires an acidic environment, therefore, the use of proton pump inhibitors or H2 receptor antagonists (H2RAs) can be problematic.[22,51]

- The most recent product label from atazanavir has specific recommendations for managing this drug interaction.[22]
- HIV treatment-experienced patients requiring a proton pump inhibitor should NOT be receiving atazanavir or atazanavir/ritonavir.
- Proton pump inhibitors used with other DHHS preferred protease inhibitors such as darunavir, fosamprenavir, lopinavir, and saquinavir are unlikely to result in reductions in HIV drug levels.[48,52-55]
- The use of H2RA can also be problematic with patients receiving atazanavir. Providers are encouraged to review the current FDA label for atazanavir or the DHHS Guideline Tables for further guidance on managing this interaction, and consider a pharmaceutical consultation.[1,22]

Lipid Lowering Medications

Hyperlidemia is a common problem with HIV treatment, especially with ritonavir-boosted protease inhibitor regimens.[4-8] As a result, treatment for hyperlipidemia is often warranted.

- The HMG-CoA Reductase Inhibitors (statins) are commonly used to treat hyperlipidemia. However, some of the drugs in the statin class are contraindicated since they are extensively metabolized by CYP3A4, similar to the protease inhibitors.
  For example, lovastatin and simvastatin are contraindicated with the PIs and the NNRTI delavirdine.[1,46]
- Pravastatatin has also been studied for the treatment of HIV-related hyperlipidemia.[47] Since pravastatin is not metabolized by CYP450, this statin is considered safest with all protease inhibitors with the exception of daraunvir.
- When darunavir was studied with pravastatin, the pravastatin levels increased nearly two-fold; therefore, pravastatin should either be avoided with darunavir/ritonavir therapy or initiated at lowest available doses and titrated cautiously.[1,48]
- When lopinavir/ritonavir was combined with rosuvastatin, the rosuvastatin AUC increased by approximately two-fold.[49,50] As a result, alternatives to rosuvastatin should be considered; if rosuvastatin is used, lowest doses should be used with close monitoring for CPK and LFT elevations.[1,50]
- Atorvastatin at low doses has been used safely for the management of HIV-related dyslipidemia and may be preferred over other statins due to its relative potency and the experience with using this statin in combination with HIV medications.[1]

IN SUMMARY, with the exception of darunavir/ritonavir, pravastatin should be considered the safest statin from a drug-interaction standpoint, given its lack of effect on CYP450.

- Simvastatin and lovastatin should be avoided in patients receiving protease inhibitors.
- Rosuvastatin, given recent concerns with concurrent use with lopinavir/ritonavir, should either be avoided or used at lowest possible doses.
- Finally, atorvastatin, when used at low doses, is likely to be an acceptable choice for patients receiving concurrent protease inhibitor therapy with close monitoring for myalgias and and other statin related toxicities.

Combinations of Antiretroviral & Other Meds TO AVOID

Psychotropics/Neuroleptics/Antidepressants

Midazolam and triazolam are contraindicated with PI or NNRTI therapy.[1]

- Concurrent use will likely increase the drug levels of midazolam and triazolam significantly, resulting in increased sedation. Therefore, these medications should be avoided and alternatives selected.
- However, recent revisions to the DHHS Guidelines provide guidance regarding the use of midazolam as a single dosage for sedation.
- In controlled settings for pre-procedural sedation, the use of midazolam is acceptable.[1]
- The neuroleptic medication pimozide should also be avoided in patients receiving protease inhibitors as well as the antidepressants fluvoxamine and nefazodone.[1]

Benign Prostatic Hyperplasia (BPH) Medications

Many of the medications used to treat BPH also are metabolized by CYP3A4.

- For example, dutasteride and alfuzosin are contraindicated with strong CYP3A4 inhibitors such as ritonavir-boosted protease inhibitors.[45,56,57]
- Other medications such as doxazosin, finasteride, tamsulosin and tolteridine are all metabolized by CYP3A4.[58-60]
- Therefore, use of these medications with concurrent protease inhibitors should be done only with close monitoring.
- Finally, the label for tolteridine (Detrol LA) does have guidelines for dosage reduction to 2 mg daily when used with strong CYP3A4 inhibitors.[60]

Anti-Seizure Medications

The first-generation seizure medications such as phenobarbital, carbamazepine and phenytoin should be avoided if possible when using PI or NNRTI based regimens.[1,48]

- Since these medications are inducers of CYP450, they can reduce concentrations of antiretroviral medications significantly.
- For example, one study of phenytoin and lopinavir ritonavir demonstrated that concurrent use resulted in a 46% reduction in lopinavir plasma concentrations.[61]
- Other potential options that are less likely to cause interactions include levetiracetam or gabapentin, since they are not cleared via CYP450.

St. John's Wort & Garlic

The use of St. John's Wort is contraindicated in patients receiving PI or NNRTI therapy.[1]

- Studies with indinavir and St. John's Wort demonstrated over a 50% reduction in indinavir concentrations.[62]
- Therefore, providers are encouraged to question patients regarding the use of herbal therapy and ensure that patients are aware that some herbal therapies may reduce levels of their HIV medications.
- Similar data has also been reported with garlic supplementation.[63]

Providers are encouraged to QUESTION PATIENTS regarding the use of herbal therapy and ensure that patients are aware that some herbal therapies may reduce levels of their HIV medications.

Role of the Pharmacist in HIV Care

PHARMACISTS CAN PLAY A CRITICAL ROLE IN HIV PATIENT CARE. Pharmacists working in the community setting filling prescriptions are often the last line of defense before the patient receives their medication. Pharmacists should be encouraging patients with HIV infection to utilize just one pharmacy for all prescriptions, especially if it is not required by their health plan. Filling prescriptions at one pharmacy allows the dispensing pharmacist to be aware of other medications that may not be prescribed by the clinician writing the HIV prescription. This allows pharmacists to screen for potential duplications in therapy and more importantly, to screen for potential drug interactions that could harm the patient. Pharmacists working in hospital or community based clinics can play a vital role in providing accurate medication histories, documentation of over the counter and herbal therapies and overall improvements in patient care.[64] In the hospital in patient setting, pharmacists have been involved in successful interventions to prevent medication errors.[65, 66] Close patient and pharmacist relationships can also be crucial in identifying and improving adherence problems that the patient may be experiencing.

CASE: HIV Treatment and the Role of the Pharmacist in Care

JH is a 38-year-old, recently diagnosed HIV-positive African-American male.

His viral load at his baseline visit was 768,000 copies/ml and his CD4 count was 286 cells/mm^3. His past medical history is significant for asthma, diabetes, HTN, hyperlipidemia, and GERD. He has no known drug allergies. He is a current smoker and admits to past history of IV drug abuse and risky sexual behavior with both men and women. He has a limited insurance plan that requires that he use generic medications when available.

Current medications include the following:

- Fluticasone/salmeterol (Advair diskus) 250/50 – one puff twice daily
- Albuterol MDI – Two puffs q6h prn wheezing/shortness of breath
- Metformin (Glucophage XR) 1g – once daily with dinner
- Hydrochlorthiazide 12.5 mg – once daily
- Lisinopril 20 mg – once daily
- Aspirin enteric coated 81 mg – once daily
- Simvastatin 40 mg –once daily at bedtime
- Omeprazole 20 mg – once daily
- Acetaminophen 650 mg – as needed for pain

The pharmacist working in the clinic pharmacy is presented prescriptions for the following HIV medications after his first visit:

- Atazanavir (Reyataz) 300 mg – one capsule once daily
- Ritonavir (Norvir) 100 mg – one capsule once daily
- Tenofovir/emtricitabine (Truvada) – one tablet once daily

After reviewing the patient's past medical history and current medication list, which of the following is true regarding the patient's initial HIV regimen?

A) It is not a preferred regimen on the current DHHS Guidelines.
B) Tenofovir/emtricitabine (Truvada) is contraindicated with concurrent lisinopril.
C) Simvastatin is likely to increase atazanavir levels and should be avoided.
D) Fluticasone should be avoided with ritonavir.

D is the correct answer.

Option A is incorrect, as this regimen is a preferred PI based regimen on the current guidelines.
Option B is also incorrect, since there is no contraindication listed for the use of tenofovir/emtricitabine with lisinopril.
Option C is also incorrect; simvastatin has not been shown to increase levels of atazanavir.
Option D is correct since case reports have demonstrated that the concurrent use of atazanavir/ritonavir is likely to cause significant increases in fluticasone blood levels which can cause iatrogenic Cushing's syndrome. In addition, salmeterol should be avoided with ritonavir.

The pharmacist calls the doctor and alerts her to the interaction with atazanavir/ritonavir and fluticasone. What should the pharmacist recommend to the provider to manage this interaction, assuming the patient is well controlled on their current asthma regimen?

A) Switch the atazanavir to darunavir, since darunavir is a new PI that is unlikely to cause this interaction.
B) Switch the atazanavir/ritonavir to saquinavir/ritonavir.
C) Switch the Advair to budesonide/formoterol.
D) Continue the current regimen and monitor the patient.

C is the correct answer.

Although darunavir/ritonavir plus tenofovir/emtricitabine is a preferred initial HIV regimen on current guidelines, the interaction with fluticasone is common for all ritonavir boosted protease options; therefore **Option A** is incorrect.
Option B is also incorrect since it is also likely to increase fluticasone levels. Also, recent warnings from the FDA regarding prolonged QT interval and other associated cardiac arrhythmias call into question the use of this medication when other options exist. In addition, it is not a preferred protease inhibitor on the current DHHS Guidelines. **Option D** is not the best choice, since continuing fluticasone and a ritonavir boosted protease inhibitor is likely to lead to a deterioration of this diabetic patient's glucose control.

In addition to the issue with fluticasone, the pharmacist also notices two other potential problems with the use of the selected HIV medications with the patient's current drug therapy. Which are they?

A) Simvastatin is contraindicated with protease inhibitors.
B) Metformin should be avoided with tenofovir due to increased risk of lactic acidosis.
C) Omeprazole will require separation from atazanavir.
D) A and C are correct.

Option D is correct.

Option B is not correct; the use of metformin is acceptable with tenofovir. Simvastatin and lovastatin are considered contraindicated with protease inhibitor based regimens and should be avoided; omeprazole will require separation from the atazanavir due to potential reductions in atazanavir level when these are taken at the same time in treatment-naïve patients. Proton pump inhibitors should not be used at all in patients who are HIV treatment-experienced. H2 receptor antagonists may be used in treatment-naïve and treatment-experienced patients, however dosage limitations and separation is likely required.

What other interventions could the pharmacist make to improve the care of this HIV infected patient?

A) Provide information regarding the avoidance of certain over the counter herbal treatments such as St. John's Wort and garlic supplements.
B) Discuss the importance of adherence to the patient's HIV regimen to maximize the efficacy of the medications.
C) Provide easy to read pamphlets and patient specific websites for obtaining additional information regarding HIV medications and their potential adverse events.
D) All of the above.

All of the above interventions would be appropriate for the pharmacist to provide to the patient to improve their HIV care.

Conclusions

The DHHS Guidelines have been recently updated to include regimens which are appropriate for patients and regimens to be avoided in HIV infection. This overview provides a summary of what should be avoided in HIV-infected patients, based upon the current treatment guidelines which were updated in December 2009. Providers should avoid regimens and components of regimens that are not recommended in the guidelines whenever possible. Though many drug interactions are not clinically significant, the ones discussed in this review are relevant and should be addressed appropriately. Finally, the pharmacist plays an important role in preventing drug interactions, avoiding prescribing errors and improving HIV medication adherence.

Table 1

Antiretroviral Regimens Recommended for Treatment-Naïve Patients[1]

Patients naïve to antiretroviral therapy should be started on one of the following three types of combination regimens:

- **NNRTI + 2 NRTIs; or**
- **PI (preferably boosted with ritonavir) + 2 NRTIs; or**
- **INSTI + 2 NRTIs.**

Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions. Refer to Table 6 for a list of advantages and disadvantages, and Appendix B, Tables 1 to 6 for dosing information for individual antiretroviral agents listed below. The regimens in each category are listed in alphabetical order.

Preferred Regimens (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use) The preferred regimens for non-pregnant patients are arranged by order of FDA approval of components other than nucleosides, thus, by duration of clinical experience.

NNRTI-based Regimen
- EFV/TDF/FTC[1]

PI-based Regimens *(in alphabetical order)*
- ATV/r + TDF/FTC[1]
- DRV/r (once daily) + TDF/FTC[1]

INSTI-based Regimen
- RAL + TDF/FTC[1]

Preferred Regimen[2] for Pregnant Women
- LPV/r (twice daily) + ZDV/3TC[1]

Comments

EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.

ATV/r should not be used in patients who require >20mg omeprazole equivalent per day. Refer to Table 14a for dosing recommendations regarding interactions between ATV/r and acid-lowering agents.

Alternative Regimens (Regimens that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)

NNRTI-based Regimens *(in alphabetical order)*
- EFV + (ABC or ZDV)/3TC[1]
- NVP + ZDV/3TC[1]

PI-based Regimens *(in alphabetical order)*
- ATV/r + (ABC or ZDV)/3TC[1]
- FPV/r (once or twice daily) + either [(ABC or ZDV)/3TC[1]] or TDF/FTC[1]
- LPV/r (once or twice daily) + either [(ABC or ZDV)/3TC1] or TDF/FTC[1]
- SQV/r + TDF/FTC[1]

Comments

NVP:
- Should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C)[3]
- Should not be used in women with pre-ARV CD4 >250 cells/mm^3 or men with pre-ARV CD4 >400 cells/mm^3

ABC:
- Should not be used in patients who test positive for HLA-B*5701
- Use with caution in patients with high risk of cardiovascular disease or with pretreatment HIV-RNA >100,000 copies/mL (see text)

Once-daily LPV/r is not recommended in pregnant women.

Acceptable Regimens (Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens.)

NNRTI-based Regimen
- EFV + ddI + (3TC or FTC)

PI-based Regimen
- ATV + (ABC or ZDV)/3TC[1]

Comments

EFV + ddI + FTC or 3TC has only been studied in small clinical trials.
ATV/r is generally preferred over ATV. Unboosted ATV may be used when ritonavir boosting is not possible

References:

[1] 3TC may substitute for FTC or vice versa.

[2] For more detailed recommendations on antiretroviral use in an HIV-infected pregnant woman, refer to ***"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,"*** at http://aidsinfo.nih.gov/guidelines.

[3] Refer to Appendix B, Table 7 for the criteria for Child-Pugh classification.

Abbreviations:

INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor
ABC = abacavir, ATV = atazanavir, 3TC = lamivudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, FPV = fosamprenavir, FTC = emtricitabine, LPV = lopinavir, NVP = nevirapine, RAL = raltegravir, r = low dose ritonavir, SQV = saquinavir, TDF = tenofovir, ZDV = zidovudine

The following combinations in the recommended list above are available as fixed-dose combination formulations:
ABC/3TC, EFV/TDF/FTC, LPV/r, TDF/FTC, and ZDV/3TC

Table 2

Antiretroviral Regimens that May be Acceptable and Regimens to be Used with Caution[1]

Regimens that may be acceptable but more definitive data are needed

CCR5-Antagonist-based Regimen
- MVC + ZDV/3TC[1]

INSTI-based Regimen
- RAL + (ABC or ZDV)/3TC[1]

PI-based Regimen
- (DRV/r or SQV/r) + (ABC or ZDV)/3TC[1]

Comments

With MVC, tropism testing required before treatment. Only patients found to have CCR-5 tropic-only virus (i.e., absence of CXCR4 tropic virus) are candidates for MVC.

Regimens to be Used with Caution

(Regimens that have demonstrated virologic efficacy in some studies, but have safety, resistance, or efficacy concerns.)

NNRTI-based Regimens
- NVP + ABC/3TC[1]
- NVP + TDF/FTC[1]

PI-based Regimen
- FPV + [(ABC or ZDV)/3TC[1] or TDF/FTC[1]]

Comments

Use NVP and ABC together with caution because both can cause hypersensitivity reactions within first few weeks after initiation of therapy.

Early virologic failure with high rates of resistance has been reported in some patients receiving NVP + TDF + (3TC or FTC). Larger clinical trials are currently in progress.

FPV/r is generally preferred over unboosted FPV. Virologic failure with unboosted FPV-based regimen may select mutations that confer cross resistance to DRV.

References:

[1] 3TC may be substituted with FTC or vice versa.

Abbreviations:

INSTI = integrase strand transfer inhibitor
NNRTI = non-nucleoside reverse transcriptase inhibitor
PI = protease inhibitor
ABC = abacavir
3TC = lamivudine
DRV = darunavir
FPV = fosamprenavir
FTC = emtricitabine
MVC = maraviroc
FPV = fosamprenavir
FTC = emtricitabine
MVC = maraviroc
NVP = nevirapine
RAL = raltegravir
r = low dose ritonavir
SQV = saquinavir
TDF = tenofovir
ZDV = zidovudine

Table 3

Antiretroviral Components Not Recommended as Initial Therapy[1]

Antiretroviral drugs or components *(in alphabetical order)*	Reasons for NOT recommending as initial therapy.
Abacavir/lamivudine/zidovudine (coformulated) as triple-NRTI combination regimen	• Inferior virologic efficacy
Abacavir + lamivudine + zidovudine + tenofovir as quadruple NRTI combination	• Inferior virologic efficacy
Abacavir + didanosine	• Insufficient data in treatment-naïve patients
Abacavir + tenofovir	• Insufficient data in treatment-naïve patients
Darunavir (unboosted)	• Use without ritonavir has not been studied
Delavirdine	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
Didanosine + tenofovir	• High rate of early virologic failure • Rapid selection of resistance mutations
Enfuvirtide	• No clinical trial experience in treatment-naïve patients • Requires twice-daily subcutaneous injections
Etravirine	• Insufficient data in treatment-naïve patients
Indinavir (unboosted)	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement
Indinavir (ritonavir-boosted)	• High incidence of nephrolithiasis
Nelfinavir	• Inferior virologic efficacy • High incidence of diarrhea
Ritonavir as sole PI	• High pill burden • Gastrointestinal intolerance
Saquinavir (unboosted)	• Inferior virologic efficacy
Stavudine + lamivudine	• Significant toxicities including lipoatrophy, peripheral neuropathy, and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
Tipranavir (ritonavir-boosted)	• Inferior virologic efficacy

Table 4

Antiretroviral Regimens or Components That Should Not be Offered AT ANY TIME[1]

Regimens Not Recommended		
Monotherapy with NRTI	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination of three or more antiretrovirals	• No exception[1]
Dual-NRTI regimens	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination of three or more antiretrovirals	• No exception[2]
Triple-NRTI regimens except for abacavir/zidovudine/lamivudine or possibly tenofovir + zidovudine/ lamivudine	• High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC or TDF/ddI/3TC, were used as initial regimen in treatment-naïve patients • Other triple-NRTI regimens have not been evaluated	• Abacavir/zidovudine/lamivudine, and possibly tenofovir + zidovudine/lamivudine, in selected patients in whom other combinations are not desirable
Antiretroviral Components Not Recommended as Part of an Antiretroviral Regimen		
Atazanavir + indinavir	• Potential additive hyperbilirubinemia	• No exception
Didanosine + stavudine	• High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women	• When no other antiretroviral options are available and potential benefits outweigh the risks
2-NNRTI combination	• When EFV combined with NVP, higher incidence of clinical adverse events seen when compared to either EFV- or NVP-based regimen. • Both EFV and NVP may induce metabolism and may lead to reductions in etravirine (ETR) exposure; thus, they should not be used in combination with ETR.	• No exception
Efavirenz in first trimester of pregnancy or in women with significant child-bearing potential	• Teratogenic in nonhuman primates	• When no other antiretroviral options are available and potential benefits outweigh the risks
Emtricitabine + lamivudine	• Similar resistance profiles • No potential benefit	• No exception
Etravirine + unboosted PI	• Etravirine may induce metabolism of these PIs, appropriate doses not yet established	• No exception
Etravirine + ritonavir-boosted atazanavir or fosamprenavir	• Etravirine may alter the concentrations of these PIs; appropriate doses not yet established	• No exception
Etravirine + ritonavir-boosted tipranavir	• Etravirine concentration may be significantly reduced by ritonavir-boosted tipranavir	• No exception
Nevirapine in treatment-naïve women with CD4 >250 or men with CD4 >400	• High incidence of symptomatic hepatotoxicity	• If no other antiretroviral option available; if used, patients should be closely monitored
Stavudine + zidovudine	• Antagonistic effect on HIV-1	• No exception
Unboosted darunavir, saquinavir, or tipranavir	• Inadequate bioavailability	• No exception

1 When constructing an antiretroviral regimen for an HIV-infected pregnant woman, consult ***"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States"*** [1] at http://www.aidsinfo.nih.gov.

2 **When considering an antiretroviral regimen to use in post-exposure prophylaxis, consult** *"Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis" in CDC MMWR Recommendations and Reports. September 30, 2005/54 (RR 09); 1–17* and *"Management of Possible Sexual, Injection-Drug-Use, or Other Non-occupational Exposure to HIV, Including Considerations Related to Antiretroviral Therapy"* in ***CDC MMWR Recommendations and Reports.*** January 21, 2005/54 (RR 02); 1-19.

Table 5 – Page 1 of 2

Drugs That Should Not be Used With PI, NNRTI, or CCR5 Antagonist Antiretrovirals[1]

DRUG CATEGORIES					
Antiretrovirals[1,2]	**Cardiac Agents**	**Lipid-Lowering Agents**	**Anti-mycobacterials**	**Gastrointestinal Drugs**	**Neuroleptics**
Atazanavir (+/– ritonavir) (ATV +/– RTV)	none	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide
Darunavir/ritonavir (DRV/r)	none	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide
Fosamprenavir (+/– ritonavir) (FPV +/– RTV)	none	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide
Indinavir (+/– ritonavir) (IDV +/– RTV)	amiodar one	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide
Lopinavir/ritonavir (LPV/r)	flecainide propafenone	simvastatin lovastatin	rifampin[4] rifapentine[3]	cisapride[5]	pimozide
Nelfinavir (NFV)	amiodarone quinidine	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide
Ritonavir (RTV)	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifapentine[3]	cisapride[5]	pimozide
Saquinavir/ritonavir (SQV/r)	none	simvastatin lovastatin	rifampin[4] rifapentine	cisapride[5]	pimozide
Tipranavir/ritonavir (TPV/r)	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide
Efavirenz (EFV)	none	none	rifapentine[3]	cisapride[5]	pimozide
Etravirine (ETV)	none	none	rifabutin (if used with ritonavir-boosted PI) rifampin rifapentine[3]	none	none
Nevirapine (NVP)	none	none	rifapentine[3]	none	none
Maraviroc (MVC)	none	none	rifapentine[3]	none	none

1 Delavirdine is not included in this table. Refer to the FDA package insert for information regarding delavirdine drug interactions.

2 Certain listed drugs are contraindicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP450 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

3 HIV patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended.

4 A high rate of grade 4 serum transaminase elevation was seen when a higher dose of ritonavir was added to lopinavir/ritonavir or saquinavir or when double-dose lopinavir/ritonavir was used with rifampin to compensate for rifampin's induction effect, so these dosing strategies should not be used.

5 The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

6 Contraindicated with oral midazolam. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

7 This is likely a class effect.

8 Concomitant use of fluticasone and ritonavir results in significantly reduced serum cortisol concentrations. Coadministration of fluticasone and ritonavir or any ritonavir-boosted PI regimen is not recommended unless potential benefit outweighs risk of systemic corticosteroid adverse effects. Fluticasone should be used with caution, and alternatives should be considered, if given with an unboosted PI regimen.

Table 5 – Page 2 of 2

Drugs That Should Not be Used With PI, NNRTI, or CCR5 Antagonist Antiretrovirals[1]

DRUG CATEGORIES

Antiretrovirals[1,2]	Psychotropics	Ergot Alkaloids (vasoconstrictors)	Herbs	Antiretrovirals	Other
Atazanavir (+/– ritonavir) (ATV +/– RTV)	midazolam[6] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[7] (various forms) ergonovine methylergonovine	St. John's wort	ETR IDV NVP	fluticasone irinotecan proton pump inhibitors (with unboosted ATV)
Darunavir/ritonavir (DRV/r)	midazolam[6] triazolam	as above	St. John's wort	none	carbamazepine phenobarbital phenytoin fluticasone[8]
Fosamprenavir (+/– ritonavir) (FPV +/– RTV)	midazolam[6] triazolam	as above	St. John's wort	ETR	fluticasone oral contraceptives
Indinavir (+/– ritonavir) (IDV +/– RTV)	midazolam[6] triazolam	as above	St. John's wort	ATV	none
Lopinavir/ritonavir (LPV/r)	midazolam[6] triazolam	as above	St. John's wort	none	fluticasone[8]
Nelfinavir (NFV)	midazolam[6] triazolam	as above	St. John's wort	ETR	none
Ritonavir (RTV)	midazolam[6] triazolam	as above	St. John's wort	none	voriconazole (with RTV >400mg BID) fluticasone alfuzosin
Saquinavir/ritonavir (SQV/r)	midazolam[6] triazolam	as above	St. John's wort	none	fluticasone[8]
Tipranavir/ritonavir (TPV/r)	midazolam[6] triazolam	as above	St. John's wort	ETR	fluticasone[8]
Efavirenz (EFV)	midazolam[6] triazolam	as above	St. John's wort	other NNRTIs	none
Etravirine (ETV)	none	none	St. John's wort	unboosted PIs, ATV/r, FPV/r, or TPV/r; other NNRTIs ATV +/– RTV	carbamazepine phenobarbital phenytoin
Nevirapine (NVP)	none	none	St. John's wort	other NNRTIs	none
Maraviroc (MVC)	none	none		none	none

Suggested Alternatives to:

- ***Lovastatin, simvastatin:*** Pravastatin and fluvastatin have the least potential for drug-drug interactions (except for pravastatin with darunavir/ritonavir, see Table 14a); atorvastatin and rosuvastatin – use with caution, start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.
- ***Rifampin: Rifabutin*** (with dosage adjustment – see Tables 14a and 14b)
- ***Midazolam, triazolam***: temazepam, lorazepam, oxazepam

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1. **A 19-year-old Hispanic, pregnant female is diagnosed with HIV during a prenatal screening appointment. Her initial viral load is 125,000 copies/ml and her CD4 count is 285 cells/mm^3.**

   Which of the following would be a preferred regimen in this setting based upon recent revisions to the DHHS Guidelines?

   A. Efavirenz/tenofovir/emtricitabine once daily
   B. Atazanavir + ritonavir and abacavir/lamivudine once daily
   C. Lopinavir/ritonavir and tenofovir/emtricitabine once daily
   D. Lopinavir/ritonavir and zidovudine/lamivudine twice daily

2. **A 44-year-old African American prisoner with a long history of HIV infection has been off of medications for about two years. He states his previous regimen was lopinavir/ritonavir in combination with stavudine and zidovudine.**

   Which of the following is true about his previous regimen?

   A. This is an acceptable regimen based upon current DHHS Guidelines.
   B. This regimen should be avoided due to a significant drug interaction between lopinavir and stavudine.
   C. This regimen should be avoided due to a significant interaction between stavudine and zidovudine.
   D. None of the above.

3. **In which of the following situations is the use of monotherapy in HIV infection acceptable?**

   A. In a treatment-naïve patient, to avoid nucleoside toxicity by using darunavir/ritonavir alone.
   B. In a treatment-experienced patient, to avoid protease inhibitor side effects by using tenofovir alone.
   C. In a pregnant woman during delivery, to prevent maternal to child transmission with intravenous zidovudine.
   D. All of the above.

4. **Which of the following statins should be avoided in patients receiving protease inhibitor-based therapy?**

   A. Simvastatin
   B. Atorvastatin
   C. Lovastatin
   D. A and C, only

5. **Which of the following NNRTIs are considered contraindicated in pregnancy?**

   A. Efavirenz
   B. Lamivudine
   C. Nevirapine
   D. Zidovudine

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6. A 28-year-old HIV infected immigrant from Myanmar is diagnosed with pulmonary tuberculosis. He could not tolerate ritonavir. His current CD4 is 281 and his viral load is undetectable after six months of efavirenz/tenofovir/emtricitabine + raltegravir.

Assuming that anti-TB medications will be initiated with rifampin, isoniazid, pyrazinamide, and ethambutol, which of the following is correct about required dosage changes to their HIV regimen?

A. Decrease efavirenz dosing to 400 mg daily.

B. Change ARV medications to dual nucleoside therapy with tenofovir/emtricitabine.

C. Increase raltegravir dosage to 800 mg BID.

D. None of the above.

7. Which of the following is true regarding the use of fluticasone with ritonavir boosted protease inhibitors?

A. There is a significant interaction with nasal fluticasone only.

B. There is a significant interaction with inhaled fluticasone only.

C. Reports of severe adrenal suppression and Cushing's syndrome are associated with concurrent use.

D. A and C only.

8. A 45-year-old Caucasian HIV infected male is on his third HIV regimen which consists of unboosted atazanavir with abacavir and lamivudine.

Which if the following is true with regards to the use of acid suppressive therapy and protease inhibitor based regimens?

A. Treatment-experienced patients should not receive proton pump inhibitors with atazanavir.

B. Darunavir/ritonavir is unlikely to interact with proton pump inhibitors.

C. Lopinavir/ritonavir is unlikely to interact with proton pump inhibitors.

D. All of the above are true.

9. Which medications or dietary supplements are contraindicated in the setting of a PI-containing regimen?

A. Beclomethasone

B. St. John's Wort

C. Rifabutin

D. Tolteridine

10. Roles that the pharmacist can play in HIV care can include which of the following:

A. Assessing adherence to HIV medications.

B. Screening for drug interactions with HIV therapy.

C. Preventing medication errors.

D. All of the above.

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PROGRAM OBJECTIVES:

Having completed this activity, are you better able to:

		Strongly Agree				Strongly Disagree
Objective 1:	List preferred, alternative/acceptable and regimens not recommended that are included in the December 2009 revision on the Department of Health and Human Services (DHHS) Guidelines for HIV treatment.	5	4	3	2	1
Objective 2:	Provide examples of common medications used in the primary care setting that should be avoided in patients receiving HIV treatment.	5	4	3	2	1
Objective 3:	Describe the role of the pharmacist in HIV care.	5	4	3	2	1
Objective 4:	Reduce medication errors through use of guidelines and/or pharmacist consultation.	5	4	3	2	1

OVERALL EVALUATION:

	Strongly Agree				Strongly Disagree
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
The program was educationally sound and scientifically balanced.	5	4	3	2	1
The program avoided commercial bias or influence.	5	4	3	2	1
Overall, the program met my expectations.	5	4	3	2	1
I would recommend this program to my colleagues.	5	4	3	2	1

Based on the content of the activity, what will you do differently in the care of your patients? *(check one)*

- ☐ Implement a change in my practice.
- ☐ Seek additional information on this topic.
- ☐ Do nothing differently. Current practice reflects activity recommendations.
- ☐ Do nothing differently as the content was not convincing.
- ☐ Do nothing differently. System barriers prevent change.
- ☐ Not applicable. I do not see patients in my current position.

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

_____

May we contact you in two months to see how you are progressing on the changes indicated above?

☐ Yes. Please provide your email address. _____ ☐ No. I do not wish to participate in the follow-up assessment.

If you are not able to effectively implement what you learned at this activity, please tell us what the system barriers are (e.g., reimbursement issues, managed care rules, formulary decisions, countervailing practice guidelines, etc).

_____

Please list any topics that you would like addressed in future educational activities.

_____

CE Activity Code: 12HC01-DE01 This form may be photocopied.

CONTINUING EDUCATION

The Role of Antiretroviral Agents in Pre and Post Exposure Prophylaxis

Release Date: June 1, 2010 • Expiration Date: June 30, 2012 • Course Code: 12HC02-DE01 • Nursing Credit for this activity will be provided through June 30, 2012.

Sponsor

Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ), Center for Continuing & Outreach Education, Division of AIDS Education.

Funding

This activity is supported by an educational grant from the New Jersey Department of Health and Senior Services (NJDHSS) – Division of HIV/AIDS Services through a MOA titled "Education and Training for Physicians and other Healthcare Professionals in the Diagnosis and Treatment of HIV/AIDS." The New York/ New Jersey AETC (AIDS Education and Training Center (NY/NJAETC) provided in-kind support through the work of its Pharmacy Director, John Faragon, PharmD, BCPS, AAHIVE.

Target Audience

This knowledge-based activity is designed for physicians, nurses, pharmacists, and other health care professionals in New Jersey who are involved in the care of persons with HIV/AIDS.

Statement of Need

In the state of New Jersey, 34,712 individuals were living with HIV/AIDS as of June 2009. According to the Centers for Disease Control and Prevention (CDC), an estimated 571,378 persons are living with HIV/AIDS in the United States. The CDC estimates that 7,000 people are infected with HIV each day on a worldwide basis. The CDC estimated HIV incidence in the United States at 54,230 in 2006. With these alarming statistics, it has become especially imperative to employ existing methods of prevention along with finding new ways to prevent HIV/AIDS. In this article, we will discuss the role of anti-retroviral therapy (ART) in both pre-exposure (PrEP) and post-exposure prophylaxis (PEP).
http://www.state.nj.us/health/aids/repa/aidsdata.shtml
http://www.cdc.gov/hiv

Learning Objectives

Upon the completion of this activity, participants should be able to:

1. Explain and implement prophylaxis for prevention of maternal-to-fetal transmission of HIV.
2. Recognize the promises and controversies behind pre-exposure prophylaxis.
3. Apply the recommendations for prophylaxis in the event of occupational exposure to HIV-infected blood and fluids.
4. Apply an algorithm to determine whether anti-retroviral therapies are needed for non-occupational exposures.

Faculty

Cindy Meng Hou, DO, MBA, is an Infectious Disease Fellow with Garden State Infectious Diseases Associates, under the auspices of Kennedy Memorial Hospital, which is affiliated with UMDNJ-Stratford.

Sindy M. Paul, MD, MPH, FACPM, is the Medical Director of the NJ Dept. of Health and Senior Services, Division of HIV/AIDS Services; Assistant Clinical Professor at the UMDNJ School of Public Health.

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Planning Committee

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- **John Faragon, PharmD, BCPS, AAHIVE,** NY/NJ AETC Clinical Pharmacy Director; pharmacist, Albany Medical Center

Method of Participation

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test which consists of a series of multiple-choice questions. Upon completing this activity as designed and achieving a passing score of 70% or more on the self-assessment test, participants will receive a letter of credit and the test answer key four (4) weeks after receipt of the self-assessment test, registration, and evaluation materials; or may complete the activity on the internet at www.umdnj.edu/ccoe. Estimated time to complete this activity as designed is 0.75 hours for physicians and 1.0 hour for nurses.

Accreditation

Physicians: UMDNJ-Center for Continuing and Outreach Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

UMDNJ-Center for Continuing and Outreach Education designates this educational activity for a maximum of *0.75 AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses: UMDNJ-Center for Continuing and Outreach Education is an approved provider of continuing nursing education by NJSNA, an accredited approver, by the American Nurses Credentialing Center's Commission on Accreditation. Provider Number P173-11/09-12. Provider Approval is valid through November 30, 2012.

This activity is awarded 1.0 contact hours.

Provider approved by the California Board of Registered Nursing, Provider Number CEP 13780.

Nurses should only claim those contact hours actually spent participating in the activity.

Review: This activity was peer reviewed for relevance, accuracy of content, and balance of presentation by Patricia Kloser, MD, MPH; Debbie Mohammed, MS, MPH, APRN-BC, AACRN; John Faragon, PharmD, BCPS, AAHIVE; and Brenda Christian, MEd, PA-C; Director of AIDS Education, UMDNJ-CCOE; and pilot tested for relevance and time required for participation by Kinshasa Morton, MD; Shobha Swaminathan, MD; Bonnie Abedini, MSN, RN; Mary C. Krug, MSN, APN; Kara Winslow, BSN, RN; Polly Jen, PharmD; Humberto Jimenez, AAHIVE; and George Rusuloj, PharmD.

Disclosure Disclaimer

In accordance with the disclosure policies of UMDNJ and to conform with ACCME and FDA guidelines, individuals in a position to control the content of this education activity are required to disclose to the activity participants: 1) the existence of any relevant financial relationship with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients, with the exemption of non-profit or government organizations and non-health care related companies, within the past 12 months; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Disclosure Declarations

There were no relevant financial relationships to disclose reported by the activity director, faculty, planning committee members, editor, content reviewers or field testers.

Off-Label Usage Disclosure

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Content Disclaimer

The views expressed in this activity are those of the faculty. It should not be inferred or assumed that they are expressing the views of NJDHSS-Division of HIV/AIDS Services, UMDNJ, or any manufacturer of pharmaceuticals. It should be noted that the recommendations made herein with regard to the use of therapeutic agents, varying disease states, and assessments of risk, are based upon a combination of clinical trials, current guidelines, and the clinical practice experience of the participating presenters. The drug selection and dosage information presented in this activity are believed to be accurate. However, participants are urged to consult the full prescribing information on any agent(s) presented in this activity for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects before prescribing any medication.

The Role of Antiretroviral Agents in Pre and Post Exposure Prophylaxis

Cindy M. Hou, DO, MBA and Sindy M. Paul, MD, MPH, FACPM

Learning Objectives

Upon completion of this activity, participants should be able to:

1. Explain and implement prophylaxis for prevention of maternal-to-fetal transmission of HIV.
2. Recognize the promises and controversies behind pre-exposure prophylaxis.
3. Apply the recommendations for prophylaxis in the event of occupational exposure to HIV-infected blood and fluids.
4. Apply an algorithm to determine whether anti-retroviral therapies are needed for non-occupational exposures.

IN THE STATE OF NEW JERSEY,

34,712 individuals were living with HIV/AIDS as of June 2009.[1]

According to the Centers for Disease Control and Prevention (CDC), an estimated **571,378** persons are living with HIV/AIDS in the United States.[2] The CDC estimates that **7,000** people are infected with HIV each day on a worldwide basis.[3] The most recent CDC estimate of HIV incidence in the United States was **54,230** in 2006.[4]

With these **ALARMING STATISTICS,** it has become especially imperative to employ existing methods of prevention along with finding new ways to prevent HIV/AIDS. In this article, we will discuss the role of anti-retroviral therapy (ART) in both pre-exposure (PrEP) and post-exposure prophylaxis (PEP).

(Continued on next page)

Release Date: June 1, 2010 • Expiration Date: June 30, 2012 • Course Code: 12HC02-DE01 • Nursing Credit for this activity will be provided through June 30, 2012.

Cindy M. Hou, DO, MBA, is an Infectious Diseases Fellow with Garden State Infectious Diseases Associates, under the auspices of Kennedy Memorial Hospital, which is affiliated with UMDNJ-Stratford.

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Sponsor: UMDNJ-Center for Continuing & Outreach Education-Division of AIDS Education.

Funding: This activity is supported by an educational grant from NJDHSS Division of HIV/AIDS Services through an MOA titled "Education and Training for Physicians and other Healthcare Professionals in the Diagnosis and Treatment of HIV/AIDS. Pharmaceutical review was provided in-kind through the New York/ New Jersey AETC.

To obtain continuing education credit, complete the quiz, registration, and evaluation on the following pages, or go to: www.umdnj.edu/ccoe/aids

Introduction to Pre-Exposure Prophylaxis

With PrEP, an individual takes ART prior to a high-risk HIV exposure, such as engaging in sexual intercourse with an individual who is known to be HIV-infected. Although the topic is controversial and research is ongoing to prove its safety and efficacy, the CDC has funded studies to explore how PrEP could work. In some relationships, women may not feel empowered to or are not allowed to use condoms for cultural or other reasons. To this regard, PrEP may be a useful female-initiated preventive measure. We will review several of the commonly asked questions and answers provided online by the CDC about PrEP.[3]

The Scientific Basis for PrEP

THE PRINCIPLES BEHIND PRE-EXPOSURE PROPHYLAXIS have historically been utilized for different disease entities. Travelers to areas endemic for malaria may be offered atovaquone/proguanil (Malarone) as preventive therapy. Individuals with a positive PPD and chest radiograph negative for tuberculosis may be offered isoniazid for treatment of latent tuberculosis.[5] In a similar fashion, with PrEP, it is thought that ART prophylaxis against HIV/AIDS could theoretically prevent the disease from occurring.

THE USE OF PROPHYLAXIS IN HIV/AIDS HAS BEEN STUDIED PREVIOUSLY AND HAS BEEN FOUND TO BE EFFECTIVE IN DIFFERENT SETTINGS.

- PEP (post-exposure prophylaxis) involves taking ART to protect against possible transmission of HIV after a high-risk exposure, such as when a healthcare worker is accidentally exposed to the blood of an HIV-infected patient through a large-bore needlestick which penetrated the skin. With PEP, there is a window of opportunity after an exposure during which ART is the most effective.[6]
- Along with cesarean section and formula feeding, the use of ART has decreased the mother-to-child transmission of HIV-1 from 25% to 1-2%.[7]
- In animal studies, monkeys who were pre-treated with tenofovir/emtricitabine (Truvada) had a degree of protection against HIV despite multiple exposures to this virus.[3]
- We will discuss occupational PEP in more detail in the section on Anti-Retroviral Therapy in Post-Exposure Prophylaxis. We will first review prophylaxis and its impact on decreasing maternal-fetal transmission of HIV/AIDS before delving into PrEP.

PROPHYLAXIS TO REDUCE MOTHER-TO-CHILD TRANSMISSION OF HIV/AIDS

PROPHYLAXIS HAS BEEN SUCCESSFULLY EMPLOYED in the setting of reduction of perinatal transmission of HIV/AIDS. In the Pediatric AIDS Clinical Trial Group Protocol 076 Study Group, when zidovudine (AZT) was given antepartum and intrapartum to the HIV infected mother and to the uninfected newborn for six weeks, the transmission was decreased by two thirds.[8] Rates of mother-to-child transmission are as low as 1% as long as a pregnant woman with HIV is managed with ART, cesarean section when appropriate, and avoidance of breast feeding.

HIV Testing in New Jersey

In the state of New Jersey, ART and other initiatives are used to prevent neonatal HIV/AIDS. As recommended by the CDC and now codified in New Jersey Public Law 2007 c218, HIV testing should be offered to pregnant women as early as possible in their pregnancy as well as again during their third trimester. If this HIV testing is not done during prenatal care, then rapid HIV testing is offered during labor and delivery. If maternal testing is still not done then mandatory newborn rapid HIV testing is required, unless parents object for religious reasons in writing.[9, 10]

In April 2009, the Perinatal HIV Guidelines Working Group published revisions to the U.S. Public Health Service Task Force's recommendations on using ART in pregnant HIV-1 infected women as well as interventions to reduce maternal-fetal transmission. The recommendations are extensively reviewed and periodically updated by this panel. For the latest updates, check the online guidelines at www.aidsinfo.nih.gov.[11]

The Working Group's recommendations included the following:[11]

- Antepartum, intrapartum, and infant ART must be provided for prevention of perinatal HIV transmission.
- If alternatives are available, breast feeding should not be employed by women with HIV, even if they are currently receiving ART.
- ART should consist of combinations of drugs, rather than single agents.
- For HIV-positive women who have detectable HIV viral RNA loads, drug resistance tests should be evaluated prior to starting or to changing ART.
- Some HIV-positive women who become pregnant may already be on a stable ART regimen that produced suppressed viral loads; these regimens should be continued except in the case of efavirenz (Sustiva) in the first trimester.

In determining an anti-retroviral regimen, providers should be aware of the FDA pregnancy category of each drug, as shown in Table 1.

Table 1. Anti-Retroviral Therapy and FDA Classifications[11]

	Drug	FDA Pregnancy Category
Nucleoside and nucleotide analogue reverse transcriptase inhibitors	Abacavir (Ziagen, ABC)	C
	Didanosine (Videx, ddI)	B
	Emtricitabine (Emtriva, FTC)	B
	Lamivudine (Epivir, 3TC)	C
	Stavudine (Zerit, d4T)	C
	Tenofovir (Viread, TDF)	B
	Zidovudine (Retrovir, AZT/ZDV)	C
Non-nucleoside reverse transcriptase inhibitors	Efavirenz (Sustiva)*	D
	Etravirine (Intelence)	B
	Nevirapine (Viramune)	B
Protease inhibitors	Atazanavir (Reyataz)	B
	Darunavir (Prezista)	C
	Fosamprenavir (Lexiva)	C
	Indinavir (Crixivan)	C
	Lopinavir/Ritonavir (Kaletra)	C
	Nelfinavir (Viracept)	B
	Ritonavir (Norvir)	B
	Saquinavir (Invirase)	B
	Tipranavir (Aptivus)	C
Entry inhibitors	Enfuvirtide (Fuzeon)	B
	Maraviroc (Selzentry)	B
Integrase inhibitors	Raltegravir (Isentress)	C

Key: * = Efavirenz can be combined with emtricitabine/tenofovir for the single agent called Atripla, which is contraindicated in the first trimester of pregnancy.

FDA PREGNANCY CATEGORY	DEFINITION
A	Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).
B	Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.
C	Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
D	Positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.
X	Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

The Perinatal Guidelines discuss treatment and prophylaxis with ART for pregnant women with HIV in several clinical situations, as outlined in Table 2, which excerpts a selection of these guidelines.

TABLE 2.
Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-1-Infected Women and Prevention of Perinatal HIV-1 Transmission in the United States[11]

Clinical Situation	Recommendation
HIV-infected woman of childbearing potential but not pregnant and who has indications for initiating antiretroviral therapy	• Initiate HAART as per adult treatment guidelines. • Avoid drugs with teratogenic potential (e.g., EFV) in women of childbearing age unless adequate contraception ensured. Exclude pregnancy before starting treatment with EFV.
HIV-infected woman who is receiving HAART and becomes pregnant	**Woman:** • Continue current HAART regimen if successfully suppressing viremia, except avoid use of EFV or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (combination d4T/ddI). • HIV antiretroviral drug resistance testing is recommended if the woman has detectable viremia on therapy. • In general, if a woman requires treatment, antiretroviral drugs should not be stopped during the 1st trimester. • Continue HAART regimen during intrapartum period (ZDV given as continuous infusion[1] during labor while other antiretroviral agents are continued orally) and postpartum. • Scheduled cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • ZDV for 6 weeks started within 6 to 12 hours after birth.[2]
HIV-infected pregnant woman who is antiretroviral naïve and has indications for antiretroviral therapy	**Woman:** • HIV antiretroviral drug resistance testing is recommended prior to the initiation of therapy and if suboptimal viral suppression after initiation of HAART. • Initiate HAART regimen. – Avoid use of EFV or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (combination d4T/ddI). – Use of ZDV as a component of the antiretroviral regimen is recommended when feasible. – NVP can be used as a component of HAART for women with CD4 count ≤250 cells/mm^3, but should only be used as a component of therapy in women with CD4 counts >250 cells/mm^3 if the benefit clearly outweighs the risk due to an increased risk of severe hepatic toxicity. • For women who require immediate initiation of therapy for their own health, treatment should be initiated as soon as possible, including in the first trimester. • Continue HAART regimen during intrapartum period (ZDV given as continuous infusion[1] during labor while other antiretroviral agents are continued orally) and postpartum. • Scheduled cesarean delivery at 38 weeks gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infant:** • ZDV for 6 weeks started within 6 to 12 hours after birth.[2]

(Continued)

TABLE 2.
Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-1-Infected Women and Prevention of Perinatal HIV-1 Transmission in the United States[11]

Clinical Situation	Recommendation
HIV-infected woman who has received no antiretroviral therapy prior to labor	**ZDV** **Woman:** • ZDV given as continuous infusion[1] during labor. **Infant:** • 2 DV for 6 weeks started within 6 to 12 hours after birth.[2] OR Combination ZDV + Single-Dose NVP **Woman:** • ZDV given as continuous infusion[1] during labor, plus single-dose NVP[3] at onset of labor. Consideration should be given to adding 3TC during labor and maternal ZDV/3TC for 7 days postpartum, which may reduce development of NVP resistance. **Infant:** • Single-dose NVP[3] plus ZDV for 6 weeks. OR **Woman:** • ZDV given as continuous infusion[1] during labor. **Infant:** • Some clinicians may choose to use ZDV in combination with additional drugs in the infant, but appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known. Consultation with a pediatric HIV specialist is recommended. • Evaluate need for initiation of maternal therapy postpartum.
Infant born to HIV-infected woman who has received no antiretroviral therapy prior to or during labor	• ZDV given for 6 weeks to the infant, started as soon as possible after birth.[2] OR • Some clinicians may choose to use ZDV in combination with additional drugs, but appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known. Consultation with a pediatric HIV specialist is recommended. • Evaluate need for initiation of maternal therapy postpartum.

3TC: lamivudine; EFV: efavirenz; NVP: nevirapine; ZDV: zidovudine

HAART: highly active antiretroviral therapy, a minimum of three antiretroviral agents;

1 ZDV continuous infusion: 2 mg/kg ZDV intravenously over 1 hour, followed by continuous infusion of 1 mg/kg/hour until delivery.

2 ZDV dosing for infants <35 weeks gestation at birth is 1.5 mg/kg/dose intravenously, or 2.0 mg/kg/dose orally, every 12 hours, advancing to every 8 hours at 2 weeks of age if >30 weeks gestation at birth or at 4 weeks of age if <30 weeks gestation at birth.

3 Single-dose NVP: Mother: 200 mg given once orally at onset of labor; Infant: 2 mg/kg body weight given once orally at 2-3 days of age if mother received intrapartum single-dose NVP, or given at birth if mother did not receive intrapartum single-dose NVP.

Excerpted from: Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. April 29, 2009; pp.1-90. Available at http://aidsinfo.nih.gov/Content Files/PerinatalGL.pdf

RESEARCH ON PRE-EXPOSURE PROPHYLAXIS

The Pre-Exposure Drugs of Interest

While there many different ART formulations to prevent maternal-fetal transmission of HIV, for pre-exposure prophylaxis, only a few agents have traditionally been studied. Most researchers have examined the impact of tenofovir/emtricitabine (Truvada). Its components include tenofovir (Viread), a nucleotide reverse transcriptase inhibitor, and emtricitabine (Emtriva), a nucleoside reverse transcriptase inhibitor. This combination has been favored by researchers because of its high potency against HIV, easy dosing, tolerable side effects, and low rates of resistance.[12] Other studies have used just tenofovir alone.

In general, tenofovir/emtricitabine is well-tolerated (see Table 1). The most common adverse effects are gastrointestinal issues such as nausea, vomiting or a loss of appetite with tenofovir. Uncommonly, renal function may be impaired, which may require simple dose adjustment. Alternatively, this medication can even result in Fanconi's syndrome, which is characterized by renal tubular injury and severe hypophosphatemia. Lactic acidosis or the presence of lactic acid in the blood can occur. Furthermore, there is loss of bone mineral density and the potential for osteoporosis. These severe but uncommon side effects are potentially reversible by stopping the drug. Of note, however, in patients who have HIV and hepatitis B, discontinuing tenofovir/emtricitabine may cause an exacerbation of hepatitis B. In one study of the effects of tenofovir in healthy individuals, there were reportedly no major side effects.[3,4]

Table 3. Side Effect Profile of Pre-Exposure Prophylaxis Medications[3,13]

	SIDE EFFECT	
Drug	Most Common	Uncommon But Serious
Tenofovir	Nausea, vomiting, loss of appetite	Fanconi's syndrome, lactic acidosis, osteoporosis
Tenofovir/emtricitabine	Diarrhea, nausea, fatigue, headache, rash	Fanconi's syndrome, lactic acidosis, osteoporosis

The Support of the Centers for Disease Control and Prevention

According to the CDC, there are several objectives in studies of PrEP. Obviously, safety and efficacy are ongoing concerns. A single solution cannot be 100% effective for preventing HIV transmission. The CDC recognizes that traditional risk-reduction strategies are still vital, and in the PrEP trials that they support, long-recognized prevention measures are being employed. Another objective is to assess adherence to daily oral medications as part of PrEP. In addition, a key issue is resistance. The CDC studies employ repeated HIV tests, and if seroconversions occur, then study pills are stopped to prevent resistance from building.[3]

As per Table 4, both the CDC and the National Institutes of Health (NIH) are sponsoring studies to examine the safety and efficacy of PrEP. The CDC has sponsored two studies taking place in the United States, including the US Extended Safety Trial (CDC4323) and the Pre-Exposure Prophylaxis Initiative (iPrEx), which also has sites in other parts of the world. Final analysis of the results for CDC4323 is anticipated sometime in the first quarter of 2010.

- In Thailand, the CDC is working with the Bangkok Metropolitan Administration and the Thailand Ministry of Public Health to evaluate the impact of once-daily oral tenofovir as PrEP for injection drug users. These patients are recruited through drug treatment centers, referrals, and community outreach clinics.
- TDF2, a study in Botswana, was originally designed to evaluate the efficacy of daily oral tenofovir/emtricitabine but failed to achieve this goal because of a low incidence of HIV infection and poor retention of participants. As a result, the focus of the study was modified to address safety and adherence. The safety and tolerability of once-daily tenofovir amongst men who have sex with men is being evaluated by the CDC, which is working with the San Francisco Department of Public Health, the AIDS Research Consortium of Atlanta, and Fenway Community Health in Boston.[3]

The NIH also is looking at two studies for PrEP. Along with the Bill and Melinda Gates Foundation, they are examining the impact of daily oral tenofovir/emtricitabine upon reducing HIV transmission in men who have sex with men. In addition, the NIH is working with the Microbicide Trials Network to examine several regimens, including daily oral tenofovir, daily oral tenofovir/emtricitabine and daily topical tenofovir gel, as PrEP for a trial involving heterosexual women.[14]

Table 4. PrEP Trials Sponsored by the CDC and NIH[14]

Study/Location	Sponsor	Population	Intervention	Enrollment
US Extended Safety Trial (CDC 4323), USA	CDC	Men who have sex with men (MSM)	Daily oral tenofovir	Completed 2009
Bangkok Tenofovir Study (CDC 4370),Thailand	CDC	Injecting drug users	Daily oral tenofovir	Ongoing through 2010
TDF2 (CDC 4940), Botswana	CDC	Heterosexual men and women	Daily oral tenofovir/ emtricitabine	Ongoing through 2010
iPrEx – Brazil, Ecuador, Peru, South Africa, Thailand, USA	NIH, Bill and Melinda Gates Foundation	MSM	Daily oral tenofovir/ emtricitabine	Ongoing through 2011
VOICE (MTN 003), South Africa, Uganda, Zambia, Zimbabwe, Other	NIH, Microbicide Trials Network	Heterosexual women	Daily oral tenofovir, Daily oral tenofovir/ emtricitabine, Daily topical tenofovir gel	Ongoing through 2011

While these patients are recruited from different setting such as clinics, community centers, and other avenues, only certain individuals are eligible candidates for the PrEP studies. First and foremost, as the idea is to prevent HIV from occurring in the first place, all of these participants are seronegative for HIV and are generally healthy. The exclusion criteria include taking any prescription medications, carrying intrauterine pregnancies and breastfeeding, and having certain comorbidities such as bone or kidney disease. Also, participants are excluded if they are already enrolled in an existing HIV trial.[3]

Financial Support for PrEP

- Overall, the Bill and Melinda Gates Foundation has invested $22.5 million in PrEP research.
- In the commercial sector, only Gilead, the manufacturer of tenofovir/ emtricitabine, has provided funds of $1.25 million.
- By one estimate, of the contributions so far, the public has provided approximately $20.6 million, with $6.3 million from the CDC, $6.3 million from USAID, and $7.7 million from NIH.[14]
- The CDC estimates that over the course of seven years, they will spend approximately $53 million on PrEP trials.
- The CDC will spend the following amounts in different geographic locations: $26 million in Botswana, $16 million in Thailand, and $11 million in the United States.[3]

CONTROVERSIES WITH PRE-EXPOSURE PROPHYLAXIS

While research is ongoing to determine the efficacy of PrEP, there are still many controversies which will likely need resolution before widespread adoption of PrEP.

Some opponents have expressed concerns over the **development of resistance.** The issue with resistance develops if the prophylactic drugs are used by an individual who seroconverts and develops HIV infection. For example, use of tenofovir may lead to a viral resistance mutation, which would then potentially limit the arsenal of ART available to an HIV-infected individual. **In ART naive patients, tenofovir resistance arises with its signature mutation, K65R.** This mutation can also cause cross-resistance to all other NRTIs except zivodudine. With emtricitabine, M184V is the mutation that confers resistance to both emtricitabine and to a structurally similar drug, lamivudine. This is why some research studies are employing a combination of tenofovir/emtricitabine in hopes that **the combination will cause less resistance than the use of a single agent.**[12]

IN CLINICAL TRIALS of PrEP, close monitoring of labwork and HIV seroconversion is possible. If PrEP is found efficacious enough to institute, then it is less clear if close monitoring will be possible. For example, to minimize drug resistance, HIV tests are completed on a frequent basis during clinical trials. In practical reality, HIV tests are not performed in a timely fashion. Furthermore, any ART use prescribed for pre-exposure prophylactic reasons would require monitoring in experienced providers' hands because of the risk of serious albeit uncommon side effects from tenofovir/emtricitabine. For example, periodically, patients would need to have their creatinine evaluated as a measure of renal function while on ART.[6]

OTHER OPPONENTS HAVE EXPRESSED CONCERN OVER POSSIBLE OFF-LABEL USAGE OF PREP. In a study performed in 2007, 227 HIV-uninfected men who had sex with men (MSM) completed interviewer-administered surveys to assess PrEP awareness.

- Of this group, one individual had previously employed PrEP by taking his HIV-infected brother's medications.
- Five individuals (2.2%) knew that a friend or sexual partner had employed PrEP.
- Awareness of PrEP in general was acknowledged by 43 (19%) of respondents.
- Their sources of information included involvement or participation with HIV prevention research or community outreach/education (44%), media outlets (21%), friends (14%), and medical providers (14%).
- Those individuals who had heard of PrEP were statistically more likely to have used PEP, had unprotected anal intercourse with a nonmonogamous male partner, used crystal methamphetamine during sex, found sexual partners online, were college-educated, and earned higher incomes.
- Overall, 86% of participants stated that if PrEP prevented HIV infection, they would be more willing to take it.[15]

Even if PrEP is found to be efficacious and adopted for use in certain high-risk populations, there is still a threat of behavioral disinhibition. This is the perception that individuals who take PrEP might mistakenly feel that they no longer need to employ other proven preventive strategies such as correctly and consistently applying condoms, engaging in safer sex, and other similar concepts. Prior to initiating PrEP, experts must continue to emphasize the importance of a multi-pronged approach to preventing HIV transmission.[16]

PrEP Case

A Serodiscordant Couple Desires to Conceive

A 35-YEAR-OLD HIV-INFECTED MALE AND HIS 32-YEAR-OLD UNINFECTED WIFE PRESENTS TO YOUR OFFICE. The HIV-infected patient has been infected with the virus for 18 years. He has been on a stable regimen of emtricitabine/tenofovir and lopinavir/ritonavir which has resulted in the latest CD4 count of 423 and an undetectable viral load. They have consistently used condoms when engaging in sexual intercourse but present today to inquire about having a child.

You counsel them about their options. Adoption, both domestic and international, is an option which they politely decline. You then discuss the technically possible but prohibitively expensive method of in-vitro fertilization requiring harvesting of his wife's eggs and his own sperm to produce an embryo, which can be either implanted into his wife or into a surrogate carrier. After careful consideration, they feel that this is not a viable plan. You then mention that they could try the natural means of conception, but in order to try to prevent his wife from contracting HIV, you feel that pre-conception ART might be necessary. In counseling this couple, you tell them that this is not a proven method of preventing the virus, but on the other hand, unprotected intercourse will provide them with their highest chances of conceiving a child. You suggest that his HIV-negative wife could be prescribed emtricitabine/tenofovir to protect her from the virus, and this drug could be taken prior to intercourse. The couple decides that they need more time to think about the risks and benefits of this option, and they are advised to return in two weeks to the clinic.

This case illustrates an hypothetical example of when pre-exposure prophylaxis could potentially be considered.

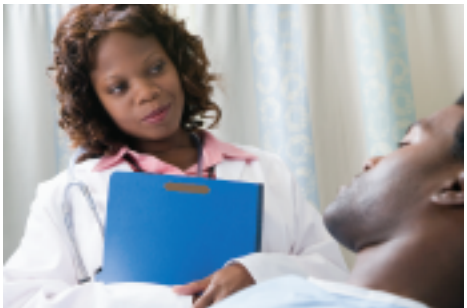
THE FUTURE OF PRE-EXPOSURE PROPHYLAXIS

Ultimately, even if research finds that PrEP is effective, it should not replace existing proven preventive strategies.[12]

PrEP could be viewed as a component of a strategy toward DECREASING HIV TRANSMISSION. This would complement interventions such as counseling to decrease the number of sexual partners, HIV counseling and testing, consistently and appropriately using condoms, diagnosing and treating sexually transmitted diseases, and employing needle exchange programs for injection drug users, amongst other initiatives.[3]

The CDC has identified several implementation issues that must be addressed, including the following:[3]

- Determine the most effective combination of interventions to decrease HIV transmission.
- Avoid excessive engagement in high-risk behaviors. A clear message will need to be communicated that PrEP, as well as any single preventive measure, is not 100% effective.
- Manage the cost burden of implementing PrEP. Some studies report that the costs of PrEP, even if targeted to 100,000 high risk individuals, would be greater than $1 billion per year. Sources of funding for PrEP need to be located.
- Ensure access to PrEP. If PrEP is advocated, then the financial afford-ability of PrEP should be addressed.
- PrEP research needs to continue in order to find what regimens are efficacious in different populations. For example, PrEP which is effective for injection drug users may not necessarily be transferable to men who have sex with men.



ANTI-RETROVIRAL THERAPY IN POST-EXPOSURE PROPHYLAXIS

Occupational Post-Exposure Prophylaxis (PEP)

Occupational PEP involves providing ART to non-HIV infected individuals in order to prevent acquisition of the virus in work settings. PEP may need to be considered in incidences where healthcare personnel are exposed to percutaneous injuries (such as with needlesticks) or contact of mucous membrane and nonintact skin with blood, tissue, and potentially infectious fluids. These fluids include cerebrospinal, pleural, peritoneal, pericardial, and amniotic. After percutaneous exposure to HIV-infected blood, the risk of HIV transmission is 0.3% and with mucous membrane exposure, the risk is 0.09%.[18] **If PEP is offered, it should be given within hours of an exposure and extended for four weeks total.** A brief summary of PEP for percutaneous injuries and for mucous membranes/nonintact skin is provided in Tables 5 and 6.

Table 5. Recommended HIV PEP for Percutaneous Injuries[18]

	INFECTION STATUS OF SOURCE PATIENT		
Exposure Type	**HIV Positive**	**HIV Negative**	**Unknown**
Less severe[1]	HIV 1: Basic 2-drug PEP HIV 2: Expanded ≥3-drug PEP	No PEP	Usually none; consider basic 2-drug PEP# if exposed to source with HIV risk factors
More severe[1]	HIV 1: Expanded 3-drug PEP HIV 2: Expanded ≥3-drug PEP	No PEP	Usually none; consider basic 2-drug PEP# if exposed to source with HIV risk factors

Key: [1] Less severe = solid needle or superficial injury.
[2] More severe = large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein.
HIV-positive, class 1 – asymptomatic HIV infection or known low viral load (e.g., <1,500 copies/mL).
HIV-positive, class 2 – symptomatic HIV infection, acquired immunodeficiency syndrome, acute seroconversion, or known high viral load.
The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP.

Table 6. Recommended HIV PEP for Mucous Membrane/Nonintact Skin Exposures[18]

	INFECTION STATUS OF SOURCE PATIENT		
Exposure type	**HIV Positive**	**HIV Negative**	**Unknown**
Less severe[1]	HIV-1: Consider basic 2-drug PEP HIV-2: Recommend basic 2-drug PEP	No PEP	No PEP
More severe[2]	HIV-1: Recommend basic 2-drug PEP HIV-2: Recommend expanded ≥3-drug PEP	Usually no PEP; consider basic 2-drug PEP for source with HIV risk factors	No PEP

Key: [1] Small volume = a few drops.
[2] Large volume = a major blood splash.
HIV-positive, class 1 – asymptomatic HIV infection or known low viral load (e.g., <1,500 copies/mL).
HIV-positive, class 2 – symptomatic HIV infection, acquired immunodeficiency syndrome, acute seroconversion, or known high viral load.
The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP.

The Public Health Service Guidelines for occupational exposure to HIV provide an appendix on ART used in PEP. While they list preferred and alternative agents for both basic and expanded regimens, we will highlight the preferred medicines in each category, as depicted in Table 7.

Table 7. Preferred ART Regimens for PEP[18]

Basic Preferred Regimens	Expanded Preferred Regimen
Zidovudine + Lamivudine = or as a combination drug, Combivir	Lopinavir/ritonavir
Zidovudine + Emtricitabine	
Tenofovir + Lamivudine	
Tenofovir + Emtricitabine, or as a combination drug Truvada	

Key: Zidovudine (Retrovir, ZDZ, AZT) • Lamivudine (Epivir, 3TC) • Emtricitabine (Emtriva, FTC) Tenofovir (Viread, TDF) • Lopinavir/ritonavir (Kaletra, LPV/RTV)

There are some anti-retroviral agents which should never be used in PEP, including the following:[18]

1) Nevirapine (Viramune, NVP) – severe hepatotoxicity, rash -> possibility of Stevens-Johnson syndrome
2) Delavirdine (Rescriptor, DLV) – rash -> possibility of Stevens-Johnson syndrome
3) Abacavir (Ziagen, ABC) – severe hypersensitivity reaction

FDA Safety Regulation

Caution: The Food and Drug Administration's (FDA) Adverse Event Reporting System Quarterly Report from October through June 2009 indicates the FDA is investigating a potential safety issue with the use of lopinavir/ritonavir for PEP. According to the report, the FDA is tracking reports of liver toxicity in patients who received lopinavir/ritonavir to reduce the risk of HIV infection after exposure.

Non-Occupational Post-Exposure Prophylaxis (nPEP)

In 2005, the CDC developed guidelines for anti-retroviral post-exposure prophylaxis after sexual, injection-drug use, and other non-occupational exposures to HIV. They defined non-occupational exposures as mucosal, percutaneous, and contact with blood or other potentially infectious body fluids exclusive of perinatal and occupationally-acquired scenarios. These authors emphasized the critical importance of behavioral modification in order to prevent HIV, and these interventions include protected sexual intercourse with a partner in a monogamous relationship, consistent and appropriate use of condoms, needle-exchange programs for injection drug users, and other similar concepts. On occasion, however, there is a need for non-occupational post-exposure prophylaxis (nPEP) with ART. While nPEP is not 100% effective, it may help to decrease the transmission of HIV.[20]

Cost-Benefit Analysis

The potential costs of nPEP include paying for medications out-of-pocket if they are not covered by insurance, and of course, having to cope with the potential side-effects of ART. Therefore, the benefits and costs should be weighed in the context of the severity of the actual exposure. A study in the United States found that there was benefit to providing nPEP in certain scenarios. This included unprotected sexual intercourse with a known HIV-infected partner or unprotected sexual intercourse (especially by the receptive anal route) with a homosexual or bisexual male of unknown HIV status. Yet, even beyond recognizing these high-risk exposures, the most cost-effective intervention is actually behavioral counseling, including risk reduction and possibly even risk avoidance.[19]

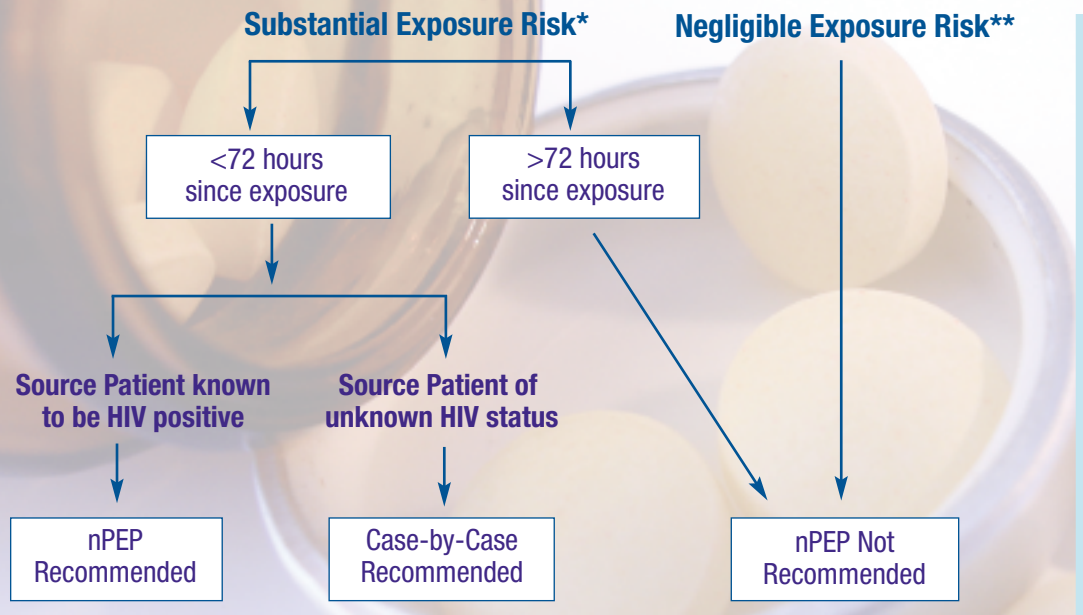
Selectively prescribing nPEP is also crucial. In many instances, nPEP is overprescribed and for reasons that are not traditionally indicated, such as a low-risk exposure where the skin was entirely intact. As one might expect, this increases the costs of prevention of HIV from $230,000 to $530,000 by one estimate.[20]

nPEP Treatment and Follow-Up

The CDC has developed an algorithm to assist providers in determining the need for nPEP, as depicted in Chart 1 below. Timing and frequency of exposure are critically important in nPEP.

- If nPEP is offered, it should be given as soon as possible after the high-risk exposure, and definitely within 72 hours because otherwise, the adverse risks from side-effects of ART may outweigh the benefits.
- Early administration of nPEP is vital because this lowers the likelihood of transmission of HIV. If the frequency of exposure is low, then ART may be helpful in reducing transmission. However, if the high-risk behaviors are habitual, such as repeated unprotected intercourse with serodiscordant couples, then nPEP should not be offered. Counseling or harm reduction should be the priority.[20]

Chart 1. Algorithm for Evaluation and Treatment of Possible Nonoccupational HIV Exposure[20]



KEY:

* **Substantial exposure risk** = exposure of vagina, rectum, eye, mouth, or other mucous membrane, nonintact skin, or percutaneous contact with blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid that is visibly contaminated with blood when the source is known to be HIV-infected.

** **Negligible exposure risk** = exposure of vagina, rectum, eye, mouth, or other mucous membrane or nonintact skin, or percutaneous contact with urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood regardless of the known or suspected HIV status of the source.

Of importance in ascertaining whether nPEP should be offered is the HIV status of the source patient.

- If the source patient has a known history of HIV and infected the exposed patient through sexual, injection-drug use, or other nonoccupational means, then consideration can be given if treatment is sought up to 72 hours of the original incident.
- Ideally, the source patient should be interviewed, and if HIV-infected, important history would include prior and current ART use and recent viral load. This may be helpful in selecting the appropriate ART for nPEP.
- If the source patient does not know his or her HIV status, then the interviewer should elicit whether there are any high-risk behaviors such as injection drug use and unprotected intercourse with multiple sexual partners.
- In some instances, after further exposure history is obtained, it may appear that the actual incident was not a high-risk exposure, and therefore, nPEP will not be necessary.[20]

nPEP Case: Assessment of Exposure

A 32-year-old Korean American male presented to the local emergency department after being "attacked" by a store customer. Upon presentation, the emergency department noted that there were scratches on the left upper extremity without any visible blood. Reportedly, the store customer had a history of intravenous drug use, but we do not know anything else about this patient. The exposed patient presented to the emergency department to inquire whether anti-retroviral prophylaxis is needed. The emergency room physician completes her initial evaluation and contacts the on-call infectious disease physician.

Upon reviewing the initial report, you ask the emergency room physician to obtain more detailed history. You specifically ask whether there was any blood initially after the attack, and there was none. No needles were purposefully injected into the exposed patient. The actual attacker ran away, and his blood is unavailable to be tested for HIV as a result. Upon your recommendation, the exposed patient is tested for HIV and hepatitis and asked to follow-up with his primary care physician. While the patient thought that this was a high-risk exposure, there was no deep penetration of skin. As a result, you recommend that prophylaxis is not required.

If a patient has a high-risk nonoccupational exposure, nPEP should be given for a 28-day course.

The selection of ART depends upon whether the source patient has virus resistant to one or more types of anti-retroviral medication. In general, however, the guidelines list several preferred and alternative agents. In Table 8, we have listed only the preferred regimens.

Table 8. Preferred Antiretroviral Regimens for Nonoccupational Postexposure Prophylaxis of HIV Infection (nPEP)

NNRTI-based	Efavirenz plus (lamivudine or emtricitabine) plus (zidovudine or tenofovir)
PI-based	Lopinavir/ritonavir (co-formulated as Kaletra) plus (lamivudine or emtricitabine) plus zidovudine

Key: NNRTI = non-nucleoside reverse transcriptase inhibitor • PI = protease inhibitor

For HIV-exposed patients, additional follow-up is required after the initial visit.

- This includes testing for HIV antibodies at baseline, 4-6 weeks, 3 months, and 6 months after exposure.
- Furthermore, tests should be provided for sexually-transmitted diseases, hepatitis B and C, and pregnancy.
- Counseling for safer sex, abstinence from injection drug use, and other behavioral modification messages should continually be employed.[20]

Conclusion

In this article, we have discussed several approaches to the use of ART to prevent rather than to treat HIV infection.

- One of the most successful measures of prevention has been the reduction of maternal-fetal transmission of HIV/AIDS as a result of providing ART during pregnancy, labor, and after birth.
- Less well known is the potential promise of pre-exposure prophylaxis in the prevention of HIV/AIDS in non-infected individuals.
- All providers should review the general principles behind post-exposure prophylaxis, whether in the occupational or non-occupational context.
- While recognizing that prophylaxis with ART is critical, we must continue to advocate for behavioral modifications to reduce the risk of HIV/AIDS transmission.

Overall, post-exposure prophylaxis is well-established as opposed to pre-exposure prophylaxis, which still has ongoing clinical trials to demonstrate its efficacy.

There are guidelines for providers on the use of ART following occupational and non-occupational exposures to HIV. In both instances, the degree of severity of the exposure as well as the HIV serostatus of the source patient should be determined, if at all possible. A careful history and physical examination may help to determine whether a given scenario is low-risk or high-risk, and this is critical in order to selectively prescribe ART for those who truly require prophylaxis. Providers must be cautioned against overprescribing ART for prophylaxis against situations which may not be warranted, such as questionable exposures to intact skin.

As for pre-exposure prophylaxis, this is an interesting HIV preventive strategy toward which the CDC, NIH, and other entities are conducting major research studies.

PrEP holds potential as an intervention that is female-driven and could potentially be used in situations where condoms are forbidden because of cultural or other reasons. Currently, however, **PrEP is not recommended for anyone and should not be employed until further research and definitive guidelines are published.** Individual patients should be counseled against use of PrEP. For now, we must wait until research solidifies the true safety and efficacy of PrEP. Even if PrEP is deemed to be effective, **we must consider that no single strategy is 100% protective and that it must be utilized in combination with known proven preventive measures.**

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CONTINUING EDUCATION

The Role of Antiretroviral Agents in Pre and Post Exposure Prophylaxis

POST TEST – Page 1 of 1

Questions refer to the content of the article and the notes that follow. To receive CME/CE/CEU credit: complete exam, registration, and evaluation forms on-line at www.umdnj.edu/ccoe/aids or fill in the forms on the following pages, and mail or fax to UMDNJ-CCOE (see Registration Form).

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1. **How long should HIV PEP be given for healthcare workers who are occupationally exposed?**
   A. 3 days
   B. 1 week
   C. 4 weeks
   D. 3 months

2. **If PEP is offered, how soon should it be provided?**
   A. After Western blot confirmation of HIV status of the source patient.
   B. After obtaining a new CD4 count and HIV viral load of the HIV-infected source patient.
   C. As close to the incident as possible.
   D. Within 24 hours.

3. **In general, which of the following anti-retroviral agents is NOT restricted in pregnancy?**
   A. Atripla
   B. Efavirenz
   C. Emtricitabine
   D. Nevirapine

4. **Which of the following is NOT a side-effect of tenofovir/emtricitabine**
   A. Fanconi's syndrome
   B. Lipodystrophy
   C. Osteoporosis
   D. Renal insufficiency

5. **A non-infected patient asks for your advice prior to engaging in recurrent high-risk sexual intercourse with a HIV-infected person. What advice do you provide?**
   A. Use tenofovir/emtricitabine just prior to intercourse.
   B. Consistently and correctly apply a condom.
   C. Take efavirenz just prior to intercourse.
   D. Obtain the resistance profile of the HIV-positive partner.

6. **A globally accepted and effective preventive strategy or strategies against HIV would include the following:**
   A. Pre-exposure prophylaxis.
   B. Employing needle exchange for injection drug users.
   C. Decreasing the number of sexual partners.
   D. Both B. and C.

7. **In the event of an occupational exposure via a percutaneous route, prophylaxis is needed in the case of:**
   A. Superficial injury, unknown HIV status of source patient.
   B. Superficial injury, known HIV-positive status of source patient.
   C. Deep penetrating injury, known HIV-positive status of source patient.
   D. Any percutaneous injury from a known HIV-positive patient.

8. **Which drugs are being evaluated as candidate drugs for PrEP?**
   A. Didanosine
   B. Tenofovir
   C. Tenofovir/emtricitabine
   D. Both B and C

9. **After a documented exposure to body fluids of a person with HIV infection, how often should the exposed person have an HIV antibody test?**
   A. Every 2 months for a year.
   B. Baseline, 4-6 weeks, 3 months, and 6 months after exposure.
   C. Every 6 months for a year.
   D. Once, after 3 weeks.

10. **In the case of nPEP, up to how many hours after the high-risk exposure should anti-retroviral medication be prescribed for prophylaxis?**
    A. 24 hours
    B. 48 hours
    C. 72 hours
    D. 96 hours

CE Activity Code: 12HC02-DE01

CONTINUING EDUCATION

The Role of Antiretroviral Agents in Pre and Post Exposure Prophylaxis

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In order to obtain continuing education credit, participants are required to:

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	1. A B C D	**3.** A B C D	**5.** A B C D	**7.** A B C D	**9.** A B C D
	2. A B C D	**4.** A B C D	**6.** A B C D	**8.** A B C D	**10.** A B C D

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CONTINUING EDUCATION

The Role of Antiretroviral Agents in Pre and Post Exposure Prophylaxis

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The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants.

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PROGRAM OBJECTIVES:

Having completed this activity, are you better able to:

		Strongly Agree				Strongly Disagree
Objective 1:	Explain and implement prophylaxis for prevention of maternal-to-fetal transmission of HIV.	5	4	3	2	1
Objective 2:	Recognize the promises and controversies behind pre-exposure prophylaxis.	5	4	3	2	1
Objective 3:	Apply the recommendations for prophylaxis in the event of occupational exposure to HIV-infected blood and fluids.	5	4	3	2	1
Objective 4:	Apply an algorithm to determine whether anti-retroviral therapies are needed for non-occupational exposures.	5	4	3	2	1

OVERALL EVALUATION:

	Strongly Agree				Strongly Disagree
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
The program was educationally sound and scientifically balanced.	5	4	3	2	1
The program avoided commercial bias or influence.	5	4	3	2	1
Overall, the program met my expectations.	5	4	3	2	1
I would recommend this program to my colleagues.	5	4	3	2	1

Based on the content of the activity, what will you do differently in the care of your patients? *(check one)*

- ☐ Implement a change in my practice.
- ☐ Seek additional information on this topic.
- ☐ Do nothing differently. Current practice reflects activity recommendations.
- ☐ Do nothing differently as the content was not convincing.
- ☐ Do nothing differently. System barriers prevent change.
- ☐ Not applicable. I do not see patients in my current position.

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

_____

May we contact you in two months to see how you are progressing on the changes indicated above?

☐ Yes. Please provide your email address. _____ ☐ No. I do not wish to participate in the follow-up assessment.

If you are not able to effectively implement what you learned at this activity, please tell us what the system barriers are (e.g., reimbursement issues, managed care rules, formulary decisions, countervailing practice guidelines, etc).

_____

Please list any topics that you would like addressed in future educational activities.

_____

CE Activity Code: 12HC02-DE01 This form may be photocopied.

NEW JERSEY June 2010
AIDSLine

UMDNJ
University of Medicine & Dentistry of New Jersey

CENTER FOR CONTINUING & OUTREACH EDUCATION
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HIV/AIDS Treatment, Training & Education Resources

New Jersey Department of Health & Senior Services – Division of HIV/AIDS Services (NJDHSS-DHAS)
(609) 984-6328 | Hotline: (800) 624-2377
www.state.nj.us/health/aids

- NJ HIV/AIDS statistical reports, regulations, forms, and links to HIV care, prevention programs, and training New Jersey rapid testing site: www.state.nj.us/health/aids/rapidtesting
- New Jersey HIV (Testing) Helpline: 1-866-HIV-CHEC
- New Jersey AIDS/STD Hotline: (800) 624-2377

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(973) 972-3690 • Fax: (973) 972-3371
www.umdnj.edu/ccoe/aids

- HIV/AIDS MEDICAL UPDATE SERIES: with funding from NJDHSS Schedule a free HIV medical education program at your health care site: contact Michelle Thompson at (973) 972-1293 ccthomps@umdnj.edu or visit www.umdnj.edu/ccoe/aids
- Conferences, training for HIV/AIDS health & social service professionals.
- Free online CME/CE for physicians, nurses, pharmacists and other healthcare professionals.

US Dept. of Health & Human Services
- HIV/AIDS treatment guidelines: www.aidsinfo.nih.gov
  National Institutes of Health database: http://clinicaltrials.gov

Centers for Disease Control (CDC) – Division of HIV/AIDS Prevention
www.cdc.gov/hiv/hivinfo.htm#WWW

- Surveillance reports, funding announcements, reporting software, epidemiology slides

HRSA: Health Resources and Services Administration of the US Department of Health and Human Services:
http://www.hrsa.gov

- HAB: HIV/AIDS Bureau of HRSA: http://hab.hrsa.gov
- TARGET Center: Ryan White Program Resources: www.careacttarget.org
- National Quality Center: initiative funded through HRSA-HAB: www.nationalqualitycenter.org

FDA MedWatch: 1-800-FDA-1088; Subscribe to e-bulletin: www.fda.gov/medwatch/elist.htm

AIDS Education and Training Center (AETC) Resources for clinicians and educators: www.aidsetc.org

National HIV/AIDS Clinicians' Consultation Center
www.ucsf.edu/hivcntr

- **Warmline:** (800) 933-3413
- **Post-Exposure Prophylaxis Hotline/PEPline:** (888) 448-4911
- **Perinatal HIV Hotline:** (888) 448-8765
- **AIDS InfoNet:** printable current HIV treatment fact sheets in several languages: www.aidsinfonet.org